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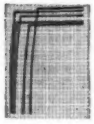

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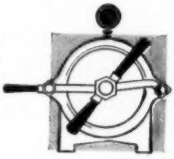

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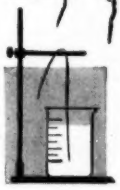

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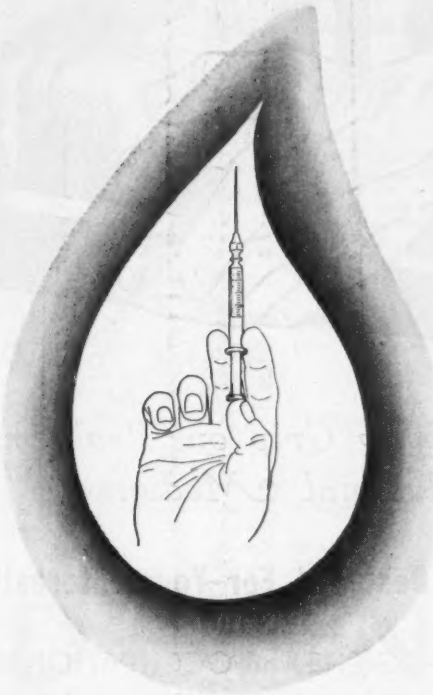

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VOLUME 62 MARCH 1951 NUMBER 3

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EFFECTS OF A WATER LOAD ADMINISTERED TO PATIENTS DURING THE IMMEDIATE POSTOPERATIVE PERIOD

The Hypotonic Syndrome

IRVING M. ARIEL, M.D.
NEW YORK

THE MAINTENANCE of an exact physical environment within the body cells is effected by the compartmental distribution of available water between the cells per se and the interstitial spaces. This separation of body water into two distinct compartments (intracellular and extracellular) represents an evolutionary development whereby the extracellular compartment absorbs the brunt of the massive influx of water and metabolites and maintains a constancy of the cellular structure which deviates little during normal states.[1]

During periods of water stress, a well integrated series of mechanisms function to cope with the particular type of stress and maintain the fluid integrity of the cell so that vital processes are not compromised.[2] Disease seriously disrupts water metabolism by producing deficits of body water (diarrhea),[3] preventing loss of body water, thereby increasing the volume (anuria),[4] or producing translocations in the intracorporeal distribution of water (malaria[5]; endocrine dysfunction).[6] That disease severely disrupts water metabolism has been known since the earliest days of recorded medical literature,[7] but that the correction of fluid irregularities is an essential of any therapeutic regimen has been stressed but recently.

In 1831 the brilliant studies of O'Shaughnessy clearly indicated that the blood of patients with cholera was deprived of water and sodium chloride, and he

From the Department of Surgery, University of Minnesota Medical School.

Aided by grants from the American Cancer Society and the Graduate School of the University of Minnesota.

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emphasized the fact that cures could be anticipated only if the water and the salt were restored to normal levels.[8] Rogers[9] and Nichols and Andrews[10] in 1909 proved conclusively the value of saline solutions during the severe epidemic of cholera in the Philippine Islands. Subsequent to that period, reports by Hartwell and Hoguet[11] and by Tileston and Comfort[12] showed that administration of sodium chloride solution was extremely important in combating disease, and a host of literature followed pertaining to the value of administration of sodium chloride.[13]

At the turn of the century, the observation that certain sick patients, especially surgical patients, would not tolerate administered salt solution was emphasized by Evans in 1911,[14] Trout in 1913[15] and later Matas in 1924.[16] Emphasis, however, was so strong concerning the complications which resulted from salt loss that the era of salt administration continued. In 1938, Coller and others formulated a clinical rule aimed at quantitatively replacing depleted sodium chloride in surgical patients.[13h]

Because of the dangers of chloride deprivation, many surgeons administered sodium chloride solution to surgical patients regardless of whether or not losses had occurred, and frequently excessive quantities of sodium chloride were administered. It was natural, accordingly, for symptoms of salt retention to become manifest and for rather dangerous clinical sequelae to develop. Since then, reports

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have appeared cautioning against the promiscuous administration of saline solution.[17] Coller and others in 1944 retracted the so-called clinical rule for chloride administration and stated that no isotonic sodium chloride solution be given during the day of operation or during the subsequent two days.[18]

Many surgeons, accordingly, have adopted the practice of administering water intravenously as a dextrose solution containing no sodium chloride. The intravenous administration of water as dextrose solution to patients postoperatively conceivably could contribute to untoward effects, especially since oliguria develops in many patients and anuria in a certain percentage subsequent to operation. Because controlled administration of fluid is germane to uncomplicated postoperative convalescence and since either a deficiency of fluid or an excess may markedly hamper recovery and contribute to serious clinical sequelae, it was considered pertinent to investigate the manner in which patients cope with a load of water containing 5 per cent dextrose (but no sodium chloride) intravenously administered during the immediate postoperative state. The experiments directed to determine this feature are the subject of the present report.

METHOD OF STUDY

The metabolism of water administered during the immediate postoperative state was investigated in 20 patients postoperatively according to the following routine: All patients were hospitalized for a variable period preceding surgical intervention, during which time they were maintained on a high carbohydrate, high protein diet with liberal quantities of fluid. Preoperative studies which included determination of weight, hemoglobin, hematocrit, total serum protein, serum chloride and carbon dioxide-combining power were made.

The operations were performed in the customary manner practiced at this institution, with no special consideration for the purposes of the study. The patients received 5 per cent dextrose in distilled water (average, 800 cc.) and citrate whole blood transfusions (average, 500 cc.), as indicated during the operation. Immediately after operation, they were weighed and blood chemical studies performed. The plasma volume and interstitial space volume were measured at this time. Blood samples as blanks were obtained in heparinized syringes, and 3 cc. of 0.05 per cent solution of Evans blue dye and 20 cc. of 5 per cent sodium thiocyanate were injected intravenously. Twenty minutes after the injection blood samples were again taken from the opposite antecubital vein for measurement of the dye dilution, and an intravenous infusion of 5 per cent dextrose in distilled water was started. Although no specific amount of fluid was given to these patients, an attempt was made to give as large a quantity as could be considered safe. The fluid ran continuously during the day of operation and the first postoperative day with a variable amount of interruption. At the completion of the fluid intake of the first postoperative day, blood chemical studies (plasma volume and the interstitial volume) were again repeated. In this manner it was hoped to note how this series of patients would

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cope with a large amount of 5 per cent dextrose in distilled water during the period immediately after surgical intervention.

Blood chemical studies were usually repeated daily for the first three postoperative days, during which time a rather high intake of water was maintained. Urine output and abnormal fluid losses were measured and the chloride content determined so that the amount of chloride lost could be known.

CHEMICAL METHODS AND CALCULATIONS

Serum chloride was determined by the technic of Schales and Schales,[19] serum protein by the method of Weichselbaum,[20] serum sodium by an internally compensated Perkins-Elmer flame photometer and the hematocrit value as described by Musser and Wintrobe.[21] The carbon dioxide–combining capacity was determined by the gasometric method of Van Slyke and Cullen.[22] Urine chloride concentration was ascertained by the modified Volhard-Harvey titration method.[22] Plasma volume and thiocyanate (available fluid) space were measured by the procedure developed by Gregersen and Stewart,[23] adapted for the Evelyn colorimeter. One postinjection sample was taken, since Noble and Gregersen have demonstrated that results so obtained vary but little from those found after taking several blood samples and projecting the dilution values to zero time.[24] The 20 minute postinjection period for withdrawal of the blood for measurement of dye dilution was taken as the most convenient point to withdraw samples for determination of both T-1824 and thiocyanate. Noble and Gregersen have shown that at 20 minutes after injection the variation from the multiple sample method is only 1 to 5 per cent.[25] The disappearance of thiocyanate continues steadily for approximately 30 minutes.[26] At 20 minutes, therefore, a compromise between the above values is achieved which permits estimation of plasma and thiocyanate volume simultaneously. Although these total values may differ slightly from those obtained by multiple technics, the method was used to compare results in the same patient at different times, and therefore comparison of values in the same patient in the different states is permitted.

In order to compute the water balance, fluid loss was measured as the quantity of urine and the amount of drainage such as aspirated gastric juice. In addition, insensible water loss was computed from the formula derived by Adolph, who observed that in ordinary circumstances 0.07 per cent per kilogram of body weight is lost per hour. The preoperative weight was utilized for these calculations.[27] The amount of water lost on the basis of this calculation will

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19. Schales, O., and Schales, S.: A Simple and Accurate Method for the Determination of Chloride in Biological Fluids, J. Biol. Chem. **140**:879, 1941.

20. Weichselbaum, T. E.: Accurate and Rapid Method for Determination of Proteins in Small Amounts of Blood Serum and Plasma, Am. J. Clin. Path., Tech. Sect. **10**:40, 1946.

21. Musser, J. H., and Wintrobe, M. M., in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, 1940, p. 795.

22. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Md., Williams & Wilkins Company, 1932, vol. 2.

23. Gregersen, M. I., and Stewart, J. D.: Simultaneous Determinations of Plasma Volume with T-1824 and the "Available Fluid" Volume with Sodium Thiocyanate, Am. J. Physiol. **125**:142, 1939.

24. Noble, R. P., and Gregersen, M. I.: Blood Volume in Clinical Shock: Mixing Time and Disappearance Rate of T-1824 in Normal Subjects and in Patients in Shock: Determination of Plasma Volume in Man from 10-Minute Sample, J. Clin. Investigation **25**:158, 1946.

25. Noble, R. P., and Gregersen, M. I.: Blood Volume in Clinical Shock: The Extent and Cause of Blood Volume Reduction in Traumatic, Hemorrhagic, and Burn Shock, J. Clin. Investigation **25**:172, 1946.

26. Stewart, J. D., and Rourke, G. M.: On the Measurement of Extracellular Fluid Volume with Thiocyanate and Body Fluid Analyses in 33 Normal Individuals, J. Lab. & Clin. Med. **26**:1383, 1941.

27. Adolph, E. F.: Physiologic Regulations, Lancaster, Pa., Science Press Printing Company, 1943.

be low because that lost by frank perspiration during and immediately after the operation was not measured. In addition, insensible water loss from exposed intra-abdominal organs during operation was probably higher than the formula utilized for these computations. Furthermore, water liberated by tissue destruction and that freed by combustion of glucose is not included in this evaluation but would constitute an additional water increment.

Failure to include these factors does not introduce serious differences, as indicated by the observation that the average weight of the patients postoperatively equaled the average preoperative weight, indicating that a state approaching isorrhea had been attained during the operation. The weight of the tissue removed was usually small (average, 100 Gm.), which feature does not prevent utilization of the patients' weights as criteria for alterations in water balance.

RESULTS

The findings are described under three headings, water balance, chloride balance and alterations in plasma and interstitial volumes. Certain patients manifested a good urinary output following the administration of water immediately after operation, while others retained a significant quantity of the fluid. The difference was one of degree. Since complications could develop on the basis of water retention, it was felt that an arbitrary division on this basis would serve to analyze more comprehensively the sequence of events which resulted from the administration of a large quantity of fluid during the immediate postoperative course. Illustrative examples are presented in table 1.

Water Balance.—The quantity of water administered to the patients is presented in table 2, and it may be noted that an average of 3,562 cc. of 5 per cent dextrose in distilled water was given on the day of operation and 3,724 cc. of fluid was administered intravenously on the first postoperative day (3,337 cc. of fluid was given to patients who manifested a good urinary output on the day of operation and 4,383 cc. on the first postoperative day). The quantity does not differ greatly from the volume of water given intravenously to the group which retained a good portion of the fluid (3,787 and 3,066 cc, respectively). The fluid was permitted to run more or less continuously; thus the amount expressed as given on the day of operation and on the first postoperative day represent usually a continuous water load with variable periods of interruption. Accordingly, an average water load of 7,286 cc. of fluid was given.

Calculations of water balance indicate that on the day of operation there was an average retention of 1,098 cc. of administered fluid by the entire group. Of the eight patients who were cataloged in the group with normal excretion, six manifested a positive water balance while two demonstrated an output greater than their intake. The net result in this group of patients was an average retention of 429 cc. of fluid. In contrast were those who retained, to a significant degree, the administered solution. Among the 12 patients who manifested this phenomenon, a net retention averaging 1,768 cc. occurred.

On the first postoperative day the water balance of all patients studied was an average net retention of 101 cc. Of the eight patients who exhibited good excretory ability on the day of operation, all but one manifested a negative balance and the average result in this group was the retention of 547 cc. of water. Of the 12 patients who retained a significant quantity of fluid on the day of operation, six continued to show a positive water balance while the other six demonstrated a negative water balance, at times to a marked degree (table 1). The net result in

TABLE 1.—*Physiological Changes Accompanying Intravenous Administration*

Patient	Age and Sex	Diagnosis and Operation	Day	Intake, Cc.	Urine, Cc.	Gastric Aspiration, Cc.	Insensible Loss, Cc.	Total Water Loss, Cc.	H_2O Balance, Cc.
								A. Examples of Patients Who	
F. R.	M 47	Carcinoma of rectum Resection and primary anastomosis	Preoperative Surgery *	 3,300	 2,010	... ...	... 936	 2,946	..... + 354
			1st	5,200	4,500	500	936	5,936	— 736
			2d	4,075	3,000	500	936	4,436	— 361
			3d	.....	.....	...	...	.....	.....
	Cumulative		.....	.....	.....	...	...	.....	— 743
J. I.	F 76	Common duct stone Cholecystectomy and exploration of common duct	Preoperative Surgery *	 4,500	 2,900	... 500	... 912	 4,312	..... + 188
			1st	3,500	2,700	1,000	912	4,612	—1,112
			2d	3,600	1,400	850	912	3,162	+ 438
	Cumulative		.....	.....	.....	...	...	.....	— 486
								B. Examples of Patients Who Manifested	
J. J.	F 71	Carcinoma of stomach Subtotal gastrectomy	Preoperative Surgery *	 3,700	 1,450	... 200	... 864	 2,514	..... +1,186
			1st	2,500	1,200	650	864	2,714	— 214
			2d	2,100	850	550	864	2,264	— 164
			3d	2,200	2,000	700	864	3,564	—1,364
	Cumulative		.....	.....	.....	...	...	.....	— 556
P. S.	M 48	Carcinoma of stomach Resection of stomach and contiguous structures	Preoperative Surgery *	 3,000	 800	... 40	... 912	 1,752	..... +1,848
			1st	3,500	450	1,100	912	2,462	+1,038
			2d	5,100	1,900	900	912	3,712	+1,388
			3d	4,000	3,200	1,400	912	5,512	—1,512
	Cumulative		.....	.....	.....	...	...	.....	+2,762

* All chemical values listed for the day of operation were obtained immediately after operation.

this group revealed an average negative water balance equaling 344 cc. The second postoperative day revealed a total negative water balance of 100 cc. and the third day a negative balance of 821 cc. for all patients studied (table 2).

The cumulative exchange of water computed for the day of operation and the first three postoperative days reveals a net increase averaging 159 cc. of fluid, with 10 patients demonstrating a positive balance and 10 demonstrating a negative balance. The interesting finding was that in the group who manifested good urinary excretion from the outset there resulted a cumulative negative balance for the period of study of 87 cc. Those who exhibited early retention of administered fluid manifested a cumulative average positive balance of 246 cc. Eight of this group of 12 patients presented a positive water balance which varied from 1,112 to 3,406 cc. (table 1 B).

Chloride Balance.—None of the patients received sodium chloride during the period of study, and the amount of the chloride lost and its reflection in the serum chloride concentration is significant. The data reveal a rather persistent and continued loss of chloride during the period of surgical intervention and the first three postoperative days (table 3).

During the day of operation, an average of 4.1 Gm. of chloride, expressed as sodium chloride, was lost in the urine by the entire series, and a similar quantity was lost by each of the two arbitrary group divisions of this study. On the first postoperative day the average urinary chloride level equaled 5.2 Gm. for the entire group and those with a good urinary output excreted 6.6 Gm., while those who were classified as retaining fluid excreted 3.9 Gm. On the second postoperative day the entire group excreted 2.3 Gm. Those with good urinary output excreted 1.6 Gm., while those who were classified as retaining fluid on the day of operation

of 5 Per Cent Dextrose in Distilled Water Postoperatively.

Chloride Output, Gm.												
Urine	Gastric Aspiration	Weight, Kg.	Hemoglobin, Gm./100 Cc.	Hematocrit, %	T.S.P., Gm./100 Cc.	Cl., mEq./Liter	CO_2 Combining Power, mEq./Liter	Na, mEq./Liter	K, mEq./Liter	Plasma Volume (Liters)	Interstitial Volume (Liters)	Comment
Maintained a Good Fluid Output												
...	...	56.0	....	....	...	107	..	...	...	...	....	
1.0	...	56.0	13.0	41.5	6.4	98	28	147	3.8	2.4	13.4	No symptoms
8.5	2.5	55.6	13.0	....	...	..	..	...	...	...	....	
1.5	2.5	54.6	13.7	43.0	6.0	96	33	144	4.6	4.5	11.2	
...	...	....	....	....	...	..	..	...	...	...	....	
—16		....	....	....	...	..	..	...	...	+2.3	— 2.3	
...	...	54.0	16.0	....	...	..	..	...	...	2.4	13.1	
18.5	2.5	55.0	14.0	46.0	...	89	23	...	...	...	....	No symptoms
4.0	5.0	54.0	....	46.0	...	84	23	...	...	2.6	13.4	
1.3	4.2	....	....	45.0	...	91	24	...	...	...	....	
—35.5		....	....	....	...	..	..	...	...	+0.2	+ 0.3	
Evidence of Water Retention												
...	...	51.7	13.5	....	5.3	106	22	...	...	...	....	
4.0	1.0	51.2	12.9	....	4.6	102	..	...	...	2.3	8.1	
2.6	3.0	52.4	13.2	43.5	...	83	17	...	...	2.9	15.6	Convulsion and coma
7.4	2.5	53.2	....	....	...	82	..	113	3.9	...	....	
2.2	3.5	51.2	13.6	45.5	4.8	76	..	...	...	...	....	
—26.2		....	....	....	...	..	..	...	...	+0.6	+ 7.5	Gradual recovery; no residual effects
...	...	54.0	14.3	44.0	7.0	108	..	...	...	2.8	13.2	
7.7	0.5	53.8	14.3	44.0	6.4	95	..	...	...	...	....	No symptoms
1.9	5.5	54.0	13.7	....	...	93	26	...	...	1.9	15.0	
2.2	4.5	53.0	13.1	....	7.1	86	..	...	...	...	....	
5.8	7.0	53.6	14.1	46.5	...	83	28	...	...	...	....	
35.1		....	....	....	...	..	..	...	...	—0.9	+ 1.8	

TABLE 2.—*Average Postoperative Alterations in Fluid Balance in Twenty Patients Who Received Intravenously 5 Per Cent Dextrose in Distilled Water*

	Total Number	Patients Who Maintained Good Urinary Exeretory Ability	Patients Who Retained Administered Fluid on Day of Operation
Number of patients	20	8	12
Average fluid given on day of surgery (cc.)	3,562	3,337	3,787
Fluid balance (cc.)	+1,098	+ 429	+1,768
1st postoperative day, fluid given (cc.)	3,724	4,383	3,066
Fluid balance (cc.)	+ 101	+ 547	— 344
2d postoperative day, fluid given (cc.)	3,397	3,367	3,423
Fluid balance (cc.)	— 100	— 98	— 108
3d postoperative day, fluid given (cc.)	3,025	3,400	2,650
Fluid balance (cc.)	— 821	—1,473	— 171
Cumulative fluid balance (cc.)	+ 159	— 87	+ 246

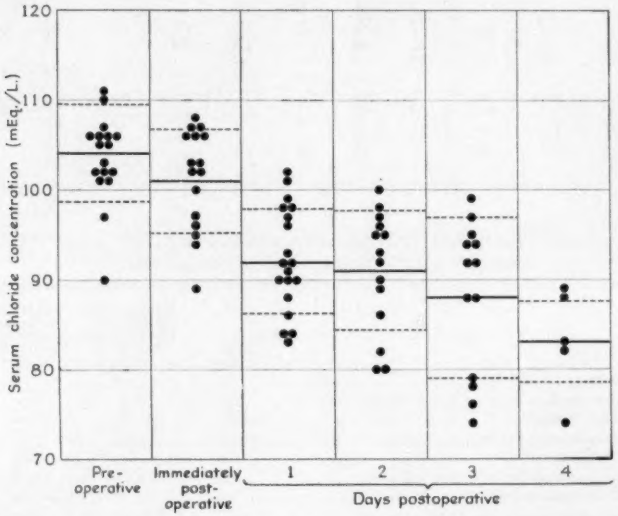
TABLE 3.—*Average Postoperative Chloride Loss Subsequent to Intravenous Administration of 5 Per Cent Dextrose in Distilled Water*

	Total Number Chloride Output, Gm.		Patients Who Maintained Good Urinary Excretory Ability Chloride Output, Gm.		Patients Who Retained Administered Fluid on Day of Operation Chloride Output, Gm.	
	Urine	Gastric Aspiration	Urine	Gastric Aspiration	Urine	Gastric Aspiration
Day of operation	4.1	1.5	4.1	2.0	4.1	1.0
1st postoperative day	5.2	3.5	6.6	4.3	3.9	2.8
2d postoperative day	2.3	3.6	1.6	3.7	3.1	3.6
3d postoperative day	3.2	4.7	4.3	4.5	2.1	5.0
Cumulative chloride loss	28.1		30.1		25.6	

excreted 3.1 Gm. The third postoperative day revealed a similar chloride excretion rate of the group, equaling 3.2 Gm. The cumulative salt loss by urinary excretion during the day of operation and the first three surgical postoperative days averaged 14.8 Gm., with a rather similar quantity excreted by each of the two groups.

This quantity of chloride excreted by patients during their postoperative course is similar to that described by Elman and his associates.[28]

That lost by gastric aspiration brings the cumulative measured chloride loss for this series of patients to 28.1 Gm. This loss is reflected in the concentration of chloride within the serum. The total changes of serum chloride concentrations are presented in the accompanying chart and demonstrate a drop in serum chloride immediately after operation and a further drop during the subsequent days. When the concentration of the serum chloride in the two groups of this study is compared,



A scatter diagram of the serum chloride concentration of surgical patients who received 5 per cent dextrose in distilled water postoperatively referred to the preoperative and postoperative values. The heavy, unbroken line represents the mean of each day, and the area between the broken lines represents the values between the plus and minus standard derivations from the mean.

a rather significant alteration is noted. The decrease of the serum chloride concentration in the eight patients who manifested a normal excretory ability revealed a rather consistent decrease, which was attributed to the chloride loss. Although the chloride loss was similar in the group which manifested retention of administered fluid, it may be noted that there is a far greater drop in their serum chloride concentration (table 4). Since this decrease in serum chloride concentration cannot be explained exclusively on the basis of chloride loss, another explanation

28. Elman, R.; Lemmer, R. A.; Weichselbaum, T. E.; Owen, J. G., and Yore, R. W.: Minimum Postoperative Maintenance Requirements for Parenteral Water, Sodium, Potassium, Chloride and Glucose, Ann. Surg. **130**:703, 1949.

for the decrement would be a hemodilution. To study this component, an analysis of variations of plasma volume and interstitial volume was performed in this group of patients.

Plasma Volume and Interstitial Volume.—The average plasma volume of the entire group under study immediately after surgical intervention was 3.0 liters. After the administration of a load of salt-free fluid an average increase to 3.4 liters was observed. An analysis of the different groups reveals that the patients who demonstrated normal urinary excretion had a plasma volume of 2.8 liters immedi-

TABLE 4.—*Alterations of Serum Chloride Concentration and Carbon Dioxide–Combining Power Subsequent to the Administration of Large Quantities of 5 Per Cent Dextrose in Distilled Water During the Immediate Postoperative Period*

	Group 1—Good Urinary Output				Group 2—Fluid Retention			
	Preoperative	Immediate Postoperative	First Postoperative Day	Second Postoperative Day	Preoperative	Immediate Postoperative	First Postoperative Day	Second Postoperative Day
Serum chloride, mEq/L.....	103.2	97.8	96.3	94.6	104.1	100.6	90.4	87.1
Serum carbon dioxide-combining power, mEq/L	26.5	....	23.0	27.0	26.2	.....	25.7	27.5

TABLE 5.—*Alterations in Plasma Volume and Interstitial Space Volume Subsequent to Administration of 5 Per Cent Dextrose in Distilled Water Postoperatively*

	Plasma Volume (Liters)	Interstitial Volume (Liters)
Total patients (17)		
Average preinfusion volume.....	3.0	12.9
Average postinfusion volume.....	3.4	14.9
Average change.....	+ 0.4	+ 1.6
Patients with good urinary excretion (5)		
Average preinfusion volume.....	2.8	13.5
Average postinfusion volume.....	3.6	12.9
Average change.....	+ 0.8	— 0.6
Patients with fluid retention (12)		
Average preinfusion volume.....	3.2	12.4
Average postinfusion volume.....	3.2	16.9
Average change.....	0.0	+ 4.5

ately after operation, but after the administration of a large quantity of fluids it had increased to 3.6 liters. The plasma volume of the group who demonstrated retention revealed no change after a load of 5 per cent dextrose in distilled water (table 5).

In contrast to these findings were the alterations in the interstitial volume. The group who manifested normal excretion revealed a postoperative interstitial volume averaging 13.5 liters, but after the administration of a large quantity of water it decreased to an average of 12.9 liters. The 12 patients who demonstrated retention revealed an opposite alteration in their interstitial volumes following the administration of salt-free fluid, with an increase from an average of 12.4 liters to the high value of 16.9 liters. This increment of 4.5 liters of water into the interstitial spaces might be a factor contributing to the retention of the administered fluid. Three patients of this group demonstrated an enlargement of the interstitial space

beyond that which could be accounted for exclusively by administered fluid and which probably represents an influx of the thiocyanate ion into the cellular compartment. This factor is discussed in more detail later in this presentation.

The notable increase in the interstitial space, as measured by thiocyanate, probably accounts for the increased drop in the serum chloride concentration presented by the patients in this group. Whether this increased thiocyanate space represents a true enlargement of the extracellular compartment or some other expansion such as increased permeability of the cells to this ion is not known, but, whatever the explanation, it reflects nevertheless an increased volume for dilution of available thiocyanate and, by inference, available chloride and demonstrates that the decreased concentration of serum chloride represents dilution of that ion, in addition to loss.

WEIGHT CHANGES

The use of the alterations in weight as a means of indicating total water exchange advocated by Wangensteen [17b] presents rather interesting indexes in this series

TABLE 6.—*Average Alterations in Water Balance, Weight and Interstitial Volume During Immediate Postoperative Period Subsequent to Administration of a Load of 5 Per Cent Dextrose in Distilled Water*

	Patients Who Maintained Good Urinary Excretory Ability	Patients Who Retained Administered Fluid
Number of patients	8	12
Calculated water balance (liters)	+ 0.4	+ 1.8
Alteration in weight (Kg.)	− 0.1	+ 1.6
Alteration in interstitial volume (liters)	− 0.6	+ 4.5

(table 6). On the morning of the first postoperative day, the average weight change in all patients studied was a net increase of 1.5 Kg. above the postoperative weight. This finding compares favorably with the total increase of an average of 1,098 cc. of water. The group classified as excreting the administered fluid retained 429 cc. of water, and there was no significant change in the average weight of this group from that observed preoperatively. In contrast, the patients who retained a significant portion of their water (1,768 cc.) averaged an increment of 1.6 Kg. above the preoperative figure. All patients of this group manifested increased weight. Although individual weights did not coincide with the computed water balance values, the over-all averages were in close agreement. The individual discrepancies might be due to inherent deficiencies of the methods employed (e. g., utilizing Adolph's formula for calculating insensible loss during the period of surgical intervention because exact determinations of insensible fluid loss could not be ascertained during this time).

The changes in the interstitial volume as measured by thiocyanate dilution revealed a decrease of 0.6 liters in the group classified as maintaining good urinary excretory ability, while those who retained fluid on the operative day revealed an increment in the interstitial space of 4.5 liters. The possibility exists that this increment possibly represents an influx of the ion into the cellular compartment. These data indicate that alteration in body weight is a more reliable criteria of

alterations in water balance than estimations of thiocyanate space because of uncertainties concerning the exact distribution of thiocyanate ion under the conditions of this experiment.

COMMENT

The data indicate that fluid administered postoperatively will be retained in part. Similar quantities of fluid administered preoperatively to the same patients will result in an excretion of the administered fluid. In fact, the administration of large quantities of water will result, usually, in an excretion of a greater quantity than that given because of the concomitant excretion of sodium chloride at the onset of the diuresis.[29] The exact mechanism responsible for the postoperative retention of water awaits elucidation. A disproportionate distribution of the fluid within the different fluid compartments of the body could be a contributing factor.

The fact that certain patients manifest a normal urinary excretion postoperatively while others do not permits an arbitrary division. This division may yield leads pertaining to postoperative complications resulting from metabolic derangements.

In this series, eight of the 20 patients studied revealed a good urinary output and this group remained in negative water balance during each day of study. In contrast, 12 patients retained administered water on the day of operation. This finding is similar to that reported by Cooper, Iob and Coller.[30] The fluid retention was not solely a replacement of fluid lost during the surgical procedure. This is evidenced by the observation that the average postoperative weight equaled the average preoperative weight, indicating that fluid replacement during surgical intervention compensated for the loss of fluids which occurred during that period. Furthermore, analysis of the specific gravity of the urine of this series of patients reveals a rather low specific gravity in all instances during the day of operation and the first postoperative day. The urine specific gravity averaged 1.013 and varied from 1.002 to 1.026 on the day of surgical intervention and averaged 1.012 and varied from 1.004 to 1.025 on the first postoperative day. There was no difference in the specific gravity of the urine in the two groups of patients. If dehydration were the cause of the observed water retention, the urinary specific gravity would have been higher. Evidence is presented also by Cooper, Iob and Coller that dehydration is not the sole responsible agent producing postoperative water retention.[30] This retention resulted in an expansion of their interstitial volumes, which averaged 4.5 liters above those preceding the administered solution. The oliguric state was transient, and at the end of the first postoperative day a good fluid output was usually observed.

Associated with the fluid retention exhibited by certain patients was a postoperative chloride loss. The average urinary loss during the day of operation and the first postoperative day equaled 9.3 Gm. of sodium chloride, with a slight diminution during the subsequent two days averaging 5.5 Gm. Thus the cumulative urinary loss for the period of study averaged 14.8 Gm. These findings are in agreement with those of Elman and others.[28] In addition, an average of 13.5 Gm. of chloride was lost during the period of study by means of gastric aspiration.

29. Stewart, J. D., and Rourke, M. G.: The Effects of Large Intravenous Infusions on Body Fluid, J. Clin. Investigation **21**:197, 1942.

30. Cooper, D. R.; Iob, V., and Coller, F. A.: Response to Parenteral Glucose of Normal Kidneys and of Kidneys of Postoperative Patients, Ann. Surg. **129**:1, 1949.

There was no significant difference in the urinary excretion of chloride of the group subdivisions of this series.

The chloride loss is reflected in the decrease of the serum chloride concentration. However, the group who had normal urinary excretion demonstrated a gradual diminution of the serum chlorides over the period of study (table 5), while the patients classified as retaining fluid manifested a more precipitous diminution in the sodium chloride concentration. As both groups excreted similar amounts of chloride, the greater decrease of serum chloride concentration in those cataloged as retaining water must be due to dilution of the available chloride. This premise is substantiated further by the observation that this group revealed an expansion of the interstitial space equaling 4.5 liters, whereas those who did not abnormally retain fluid demonstrated an average diminution of the interstitial volume of 0.6 liters. Water administered without salt has been demonstrated to diminish the interstitial space.[29] Its expansion in many of the patients of this series following the administration of ion-free fluid probably represents an abnormality of water metabolism.

The diminution of serum chloride concentration accordingly represents in part a greater dispersion of the ion within the interstitial compartment. It is of interest in this respect that the plasma volume did not alter proportionately with the changes in interstitial volume, and the disproportionate variation of these compartments indicates that the plasma volume cannot be used as an indicator for volume alterations of the extracellular compartment.

It has been observed that intravenously administered dextrose solutions apparently set into motion a series of mechanisms which attempt to retain the electrolyte composition of the extracellular fluid. This is effected by the excretion of large amounts of salt-poor urine. When the water load is greater than can be regulated by renal control, chloride excretion and water retention will occur. This is believed to be the mechanism for production of the symptoms of water intoxication.[29] A water content greater than the normal quantity within the body can be attained in man by giving 20 to 200 cc. of water every 10 minutes. The intake usually exceeds the output for about two hours, after which the output is greater by 8 per cent than the intake. This is due to the excretion of chloride with the resultant deficiency of salt.[31] If salt, 0.14, 0.6 or 1.7 per cent, is contained in the ingested fluid, a state of isorrhea (the output equals the intake) will be achieved.[2]

Water diuresis is temporarily inhibited by vomiting produced by any of a number of different emetics[2] (by producing a reflex change in the renal blood flow), by syncope which follows prolonged maintenance of erect posture in man[32] and by adrenal dysfunction. In adrenalectomized animals,[33] the water diuresis mechanism fails completely, and the retention is usually considered to be due to an overactive reabsorption of water by the kidneys.

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31. Wolf, A. V.: The Dehydrating Effect of Continuously Administered Water, Am. J. Physiol. **143**:567, 1945.

32. Brun, C; Knudsen, E. O. E., and Rasschou, F.: Post-Syncopal Oliguria, Kidney Function and Circulatory Collapse, Acta med. Scandinav. **122**:381, 1945.

33. Liling, M., and Gaunt, R.: Acquired Resistance to Water Intoxication, Am. J. Physiol. **144**:571, 1945. Shipley, R. A.: Cause of Abnormal Retention of Ingested Water in Adrenalectomized Rats, Endocrinology **36**:118, 1945.

Kourilsky and others [34] have described a syndrome in man, producing water retention, which they believe is the result of a pathological state of hypophysis secreting an excessive antidiuretic hormone. High doses of water do not elicit a diuretic response in this syndrome.

A new clinical entity termed "thermogenic anhidrosis" [35] has been observed in soldiers while training in the American desert, and a similar condition has been observed when patients are exposed to artificial fever.[36]

The mechanism for failure of water diuresis in certain patients postoperatively following administration of water is not known but is probably related to hormonal imbalance. Previous studies from this clinic have indicated that in most surgical patients little abnormality in kidney function exists immediately after operation as manifested by relatively normal values in renal plasma flow, glomerular filtration rate or tubular function.[37]

The data indicate, furthermore, that in most instances water retention is transient, and it is during the period immediately after a surgical procedure that the patient is most susceptible to the danger of excess fluid administration, including symptoms of water intoxication. Three patients of this series suffered from symptoms of water intoxication during this study.

Convulsions.—Convulsions produced by water excesses are accompanied with unusual brain waves.[38] McQuarrie has studied intensively the mechanism of convulsions in epileptic patients and has shown that a state of excess hydration or mild alkalosis may be an important factor in the causation of epileptic seizures.[39] A deficit in the body water, no matter how produced, does favor the cessation of seizures, while a positive water balance tends to cause their recurrence.[40] It is McQuarrie's belief that possibly the brain cells of the epileptics are characteristically oversensitive to dilution of the extracellular fluid and that the conditions which induce seizures, such as alkalosis, mechanical injury, anoxia or nervous excitation, increase cell membrane permeability. He further presents evidence that an abnormal leakage of potassium occurs from the cells during the periods of rehydration, which is contributory evidence of the existence of a defective cell membrane.[39] A situation akin to these mechanisms may prevail in certain patients during the immediate postoperative state. A diminished ability to excrete water subsequent to administration of a water load immediately after operation results in the retention of a hypotonic fluid mass. This is probably a factor which pro-

34. Kourilsky, R.: La pathogénie du diabète insipide humain, Bull. Acad. de méd. **126**:293, 1942.

35. Wolkin, J.; Goodman, J. I., and Kelley, W. E.: Failure of the Sweat Mechanism in the Desert: Thermogenic Anhidrosis, J. A. M. A. **124**:478 (Feb. 19) 1944.

36. Brown, H. R., Jr.; Clark, W. F.; Jones, N.; Walter, J., and Warren, S. L.: Relationship of Dehydration and Over-Hydration of Blood Plasma to Collapse in Management of Artificial Fever Therapy, J. Clin. Investigation **22**:471, 1943.

37. Ariel, I. M., and Miller, F.: Effects of Abdominal Surgery upon Renal Clearance, Surgery **28**:716, 1950.

38. Gellhorn, E., and Ballin, H. M.: Water Intoxication and the Electroencephalogram, Am. J. Physiol. **146**:559, 1946.

39. McQuarrie, I.: Some Contributions of Biochemistry to the Study of Epilepsy, J. Chem. Education **10**:205, 1933.

40. Forbes, W. H.; Dill, D. B., and Hall, F. G.: Effect of Climate upon Volumes of Blood and Tissue Fluid in Man, Am. J. Physiol. **130**:739, 1940. McQuarrie.[39]

duced the convulsions in three of the patients in this series and in the other patients not included in this series whose histories are appended. This situation is similar also to that described by Schroeder in cases of renal failure associated with low extracellular sodium chloride. He believes that excessive depletion of body salt and retention of water with dilution of the available salt results in renal failure.[41] Studies described previously tend to substantiate this claim, because withdrawal of chloride with adequate replacement of fluid resulted in a pronounced diminution of the renal plasma flow and the glomerular filtration rate.[42] Schroeder described this condition essentially in patients with cardiovascular diseases who were on a salt-free diet and in whom additional losses were induced by mercurial diuretics. The entity has been described further in patients with cardiovascular disturbances by MacGuire [43] and Soloff and Zatuchni.[44] The last authors stress the fatal outcome which may result.

In view of observations that retention of large quantities of isotonic salt solution has not produced the symptoms of water intoxication, the clinical picture must accordingly be a manifestation of hypotonicity rather than of edema exclusively, and the term "hypotonic syndrome" describes more adequately this entity, whereby the excretion of chloride combined with the retention of water produces an expanded, hypotonic, extracellular compartment. This is most likely the mechanism which produced convulsive seizures in some of the patients. Certain patients, however, with as severe a degree of retained hypotonic fluid may complain only of a feeling of weakness or manifest no symptoms. The mechanism for these differences in clinical response is not entirely clear but may be due in part to the status of the central nervous system as the target organ for producing the convulsions. There were no criteria in the group of patients under study to indicate which of them would retain fluids and, of those who did retain fluids, which would have convulsions.

Recently at the Mayo Clinic postanesthetic encephalopathy which was observed in two patients and was thought to be due to cerebral edema was treated with hypertonic human albumin solution, with good clinical responses. The quantity of fluids given is not mentioned, but these cases may represent the entity described here, with anoxia acting as a contributory factor.[45]

The Expanded Interstitial (Thiocyanate) Space.—A rather interesting finding in several patients in this series was the great degree of expansion of the interstitial space, which could not be explained solely by the quantity of fluid administered or by the shift of water from the intracellular compartment into the

41. Schroeder, H. A.: Renal Failure Associated with Low Extracellular Sodium Chloride: Low Salt Syndrome, J. A. M. A. **141**:117 (Sept. 10) 1949.

42. Ariel, I. M., and Miller, F.: The Effects of Hypochloremia upon Renal Function, Surgery **28**:552, 1950.

43. MacGuire, W. B., Jr.: Risk of Uremia Due to Sodium Depletion, J. A. M. A. **137**: 1377 (Aug. 14) 1948.

44. Soloff, L. A., and Zatuchni, J.: Syndrome of Salt Depletion Induced by Regimen of Sodium Restriction and Sodium Diuresis, J. A. M. A. **139**:1136 (April 23) 1949.

45. Seldon, T. H.; Faulconer, A., Jr.; Courtin, R. F., and Pino, D. M.: Postanesthetic Encephalopathy: The Postulation of Cerebral Edema as a Basis for Rational Treatment, Proc. Staff Meet., Mayo Clin. **24**:370, 1949.

interstitial space. One detailed report of a case of expanded interstitial space associated with convulsions and coma (table 2, case 2) will serve to exemplify this phenomenon.[46]

J. J., a 71 year old white woman, was admitted to the University Hospital on July 24, 1949, with a diagnosis of adenocarcinoma of the stomach, hydronephrosis on the left and cholelithiasis. She had a history of mild paralysis agitans (parkinsonism) of six years' duration for which she had never received therapy. There was no history of encephalitis and no other symptoms involving the central nervous system. On admission her blood pressure was 140 mm. of mercury systolic and 90 diastolic. The heart was of normal size, and an electrocardiogram was normal. Her venous pressure was 8 cm. of sodium citrate, and the vital capacity equaled 2.4 liters. A study of the phenolsulfonphthalein excretion of the kidneys revealed 76 per cent excretion 120 minutes after injection and 44 per cent excretion 30 minutes subsequent to the administration.

On July 28, 1949, the patient was subjected to subtotal gastrectomy, nephrectomy and cholecystectomy under gas, oxygen and ether anesthesia. The operation lasted four and a half hours, and during this interval she received 500 cc. of whole blood and 700 cc. of 5 per cent dextrose in distilled water. During the remainder of the day she received 3,000 cc. of 5 per cent dextrose in distilled water. Her urine output for the day of the operation was 1,450 cc., with a specific gravity of 1.021. She was given a total intake of 3.7 liters of 5 per cent dextrose and distilled water on the operative day and 2.5 liters the subsequent day. She excreted 1,200 cc. of urine, with a specific gravity of 1.024 and a chloride content of 3.3 Gm. per liter, on the day after operation. Her immediate postoperative course was satisfactory. On the evening of the first postoperative day a generalized tonic spasm suddenly developed, followed by generalized clonic convulsions which lasted for about a half minute. No respirations were observed during this period, and she became cyanotic. Before the convulsive seizure she had been lethargic, and the convulsions occurred shortly after attempts to arouse her. Immediately after the convulsions, she became entirely unresponsive. Her blood pressure remained 120 mm. systolic and 60 mm. diastolic and her pulse rate continued at 60 beats per minute and became irregular. Her skin was cold and clammy; Hoffman's sign was negative, but bilateral positive Babinski signs developed. The left eye deviated externally and the pupils reacted to light and in accommodation. The abdomen was soft. The knee jerk and ankle jerk reflexes were absent bilaterally. A second generalized grand mal type of seizure occurred about two hours after the first one, after which the patient became completely areflexic. A lumbar puncture performed on the second postoperative day revealed a pressure of 140 cc. of water. The protein content equaled 2 Gm. per 100 cc., glucose 77 mg. per 100 cc. and chlorides 104 milliequivalents per liter. The serum chloride, which had been 108 milliequivalents per liter during the immediate postoperative period, descended to 83 milliequivalents at the time of the first convulsive seizure. At this time the serum carbon dioxide–combining power equaled 17 milliequivalents per liter. On the second postoperative day the serum sodium was 113 milliequivalents per liter and the potassium 3.9 milliequivalents per liter. The exact interpretation of the situation was uncertain, but it was believed by some to be on the basis of a cerebral vascular accident.

A rather interesting observation was the alteration in the thiocyanate (interstitial) space. Immediately after operation, the plasma level was 2.3 liters and the fluid in the interstitial space 8.1 liters. On the first postoperative day (before the onset of convulsions) the plasma volume had increased slightly to 2.9 liters but the interstitial volume had practically doubled to the high value of 15.6 liters. This increment of 7.5 liters, not entirely the result of administered fluid, indicates that either an influx of intracellular water into the interstitial spaces had occurred or that the cellular membrane impermeability to thiocyanate had been disturbed.

The patient was treated with hypertonic dextrose solutions intravenously, which induced a diuresis. On the morning of the fourth postoperative day her plasma volume was 3.6 liters and the interstitial space volume had diminished to 9.6 liters. She became responsive, manifested no residual disturbance of the central nervous system and on the ninth day began to eat normally. She was discharged on the fourteenth postoperative day.

46. Ariel, I. M.; Kremen, A. J., and Wangensteen, O. H.: An Expanded Interstitial (Thiocyanate) Space in Surgical Patients, Surgery **27**:827, 1950.

Several other patients manifested significant expansion of the interstitial space, usually to a marked degree. Increases in extracellular compartments may occur after the administration of large volumes of isotonic solutions of sodium chloride,[29] heart failure,[47] eclampsia [48] or the administration of 5 per cent dextrose in water if urinary excretion is prevented.[49]

The reason for the expanded interstitial spaces in the patients herein presented is not extirely manifest. It has been demonstrated that in certain patients the cellular membrane has become permeable to the thiocyanate ion, permitting the ingress of that ion and water into the intracellular compartment. Since thiocyanate is believed to simulate chloride in its distribution,[50] it follows that chloride also has been permitted to transgress the cellular barrier. The thiocyanate space, therefore, under these conditions does not measure the extracellular compartment in its strict sense, for a segment of the intracellular compartment may be included in the measurement.

A decrease in the concentration of serum chloride which cannot be accounted for by excretion suggests that a corporeal redistribution of the electrolyte, which is usually situated in an extracellular location, has occurred. Intracellular ingress of chloride and thiocyanate has been described in various conditions,[51] and its probable occurrence in the patients of this series implies a clinical significance in surgical patients.

In summary, therefore, one might interpret the sequence of events which occurred in the patients herein presented as follows: As a result of the trauma of surgery and/or anesthesia, a state of immediate postoperative oliguria occurred. Water given to the patients was retained in part, with an increased dilution of the existing blood crystalloids. If administration of water had been continued, the degree of retention might have become significant. The oliguric state of this series was transient. A certain number of patients did not reveal any oliguria after operation and excreted the administered fluid in a normal manner.

Convulsions developed in a certain group of patients who retained water. The reason why certain patients suffered convulsions and others who retained as great a quantity of water did not is enigmatic, but the probability is that either preexistent damage to the central nervous system (paralysis agitans), as demonstrated by one of these patients, or possibly anoxia or other damage to the brain rendered

47. Schwartz, I. L.; Schachter, D., and Freinkel, N.: The Measurement of Extracellular Fluid in Man by Means of a Constant Infusion Technique, J. Clin. Investigation **28**:1117, 1949.

48. Freis, E. D., and Kenny, J. F.: Plasma Volume, Total Circulating Proteins and "Available Fluid" Abnormalities in Pre-Eclampsia and Eclampsia, J. Clin. Investigation **27**:283, 1948.

49. MacQuarrie, I.; Hansen, A. E., and Ziegler, M. R.: Studies on the Convulsive Mechanism in Idiopathic Hypoparathyroidism, J. Clin. Endocrinol. **1**:789, 1941. Elkinton, J. R.; Winkler, A. W., and Danowski, T. S.: The Importance of Volume and of Tonicity of the Body Fluids in Salt Depletion Shock, J. Clin. Investigation **26**:1002, 1947.

50. Winkler, A. W.; Elkinton, J. R.; Hopper, J., and Hoff, H. E.: Experimental Hypertonicity: Alterations in the Distribution of Body Water and the Cause of Death, J. Clin. Investigation **22**:107, 1944.

51. Overman, R. R.: Permeability Alterations in Disease, J. Lab. & Clin. Med. **31**:1170, 1946. Amberson, W. R.; Nash, T. P.; Mulder, A. G., and Binns, D.: The Relationship Between Tissue Chloride and Plasma Chloride, Am. J. Physiol. **122**:224, 1938. Manery, J. F.: The Fate of Injected Radioactive Chlorine, Am. J. Physiol. **129**:417, 1940.

the brain cells more permeable to water and more sensitive to excitation. In addition, an entity is described in which an apparent breakdown in the carefully regulated mechanism of ionic exchange between the intracellular and extracellular compartment appears to have occurred. The expansion of the thiocyanate space, which could not be explained on the basis of a pure physical expansion of the extracellular compartment, indicates strongly that the cell membrane had become permeable to the thiocyanate ions and probably also the chloride and sodium ions. The exact cause of this entity and its nature and clinical implications are now being investigated.

On the basis of this hypothesis, the following therapeutic regimen is presented for combating the convulsions followed by coma in surgical patients during their immediate postoperative period.

Therapy: The best therapy, of course, is prophylaxis. Anoxia or any other mechanism damaging to the central nervous system should be carefully avoided. In certain patients with diseases of the central nervous system, such as paralysis agitans, epilepsy, parathyroid disease and others, much closer attention must be paid to the state of hydration. Attempts must be made to prevent overhydration of these patients, with special emphasis on prevention of increased dilution of the available electrolytes.

The most critical period for the onset of clinical sequelae from hydration abnormalities appears to be the first postoperative day. Most convulsive seizures were noted on the first day after the operation in this clinic. A combination of central nervous system and renal abnormalities is probably the accountable feature.

The treatment of a patient in whom convulsions and semiconsciousness have developed resolves itself about two factors: correction of the hypotonicity and reduction of the fluid increment. The correction of the hypotonicity as a primary objective by administration of salt and water would result in an aggravation of the edema. It is felt, accordingly, that effort should be directed first toward the elimination of fluid. This has been done in the cases of this series by the intravenous administration of 50 and 20 per cent dextrose solutions in distilled water. In most instances, diuresis ensued. If additional excretion was required, it was accomplished by the administration of plasma solution, preferably in a concentrated form. After an adequate quantity of fluid had been withdrawn from the organism, saline solution in the form of 0.9 per cent sodium chloride was given. Chabanier and Lobo-Onell have described a similar condition with an associated azotemia, and these authors advocate an administration of a hypertonic saline solution.[52] However, the use of a hypertonic salt solution may disrupt the intracellular-extracellular fluid and solute balance, producing thereby an aggravated derangement of intracellular metabolism. It therefore seems preferable to bring about dehydration of the patient first and use an isotonic solution for replacement.

In instances in which anuria and oliguria persist postoperatively extreme caution must be exercised to prevent overhydration. A combination of alterations of the central nervous system and abnormalities of hydration focuses attention on the fact that ionic free fluid must be given cautiously to the postoperative patient.

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52. Chabanier, H., and Lobo-Onell, C.: Hypochlorémie et accidents postopératoires: Étude clinique, pathogénique et thérapeutique, Paris, Masson & Cie, 1934.

SUMMARY AND CONCLUSIONS

1. A water tolerance test is described which was utilized in 20 patients to study the metabolism of a load of water containing 5 per cent dextrose administered after a major surgical procedure.

2. After the administration of an average of 3,562 cc. of 5 per cent dextrose in distilled water in postoperative patients, an average retention of 1,098 cc. was demonstrated by the entire group on the day of operation. Eight patients were cataloged as having normal excretion, and these patients retained but 429 cc. of fluid, in contrast to 12 who were classified as retaining fluid, with an average of 1,768 cc. The retention of water, however, was but transient and the cumulative exchange of water considered for the day of operation and the first three postoperative days revealed a net increase averaging 159 cc. In several patients the cumulative postoperative water retention was severe and varied from 1,112 to 3,406 cc.

3. The two subgroups of this presentation, namely, those who manifested retention of water on the day of operation and those who did not, reveal a similar excretion of chloride. The cumulative salt loss by urinary excretion during the day of operation and the first three postoperative days averaged 14.8 Gm. The chloride loss by gastric aspiration equaled 13.3 Gm. of sodium chloride, which brings the cumulative measured chloride loss for this series of patients to 28.1 Gm. for the day of surgical intervention and the first three postoperative days.

4. The average plasma volume of 3.0 liters for the entire group noted postoperatively increased to 3.4 liters after the administration of a large amount of 5 per cent dextrose in distilled water. However, those who demonstrated normal urinary excretion had an increase of 0.8 liters after the fluid adminstration, with no change whatsoever noted in those who retained the administered fluid. In contrast, the interstitial space (the extracellular space as measured by thiocyanate, with the plasma volume subtracted) averaged 13.5 liters for those who manifested a normal excretory ability, and this average decreased to 12.9 liters subsequent to the intravenous administration of fluid. The 12 patients who demonstrated retention revealed an opposite alteration in their interstitial volume, with an increase from 12.4 liters to the high value of 16.9 liters after the intravenous administration of fluid.

5. The postoperative hypochloremia can be explained accordingly, partly on the basis of chloride loss and partly on the basis of greater distribution of the chloride ion as a result of fluid retention, especially within the interstitial spaces.

6. The fact that patients postoperatively retain administered fluid, whereas normally it would be excreted and, in reality, a greater amount would be excreted than is administered, indicates an abnormality in the metabolism of 5 per cent dextrose in distilled water postoperatively which is not a result of intrinsic damage to the kidney per se.

7. The entity wherein the normal regulatory mechanism of permitting but a slight quantity of chloride to enter the cells is disrupted, with a breakdown of the permeability of the cells and an abnormal intracellular ingress of that ion, is discussed.

8. The convulsions noted postoperatively can be described as follows: Salt loss, which occurs after operation, plus the administration of large quantities of ion-free water, with the resultant retention of that water, produces an increased water volume and dilution of the available electrolytes. The hypotonicity of the fluid results in the clinical sequelae noted, with subsequent convulsions. In certain patients who have brain damage, as manifested by paralysis agitans (as in one patient of this series), severe arteriosclerosis or damage produced by anoxia or other surgical trauma, there exists an abnormal permeability of the cells to the water, which augments the intracellular edema and facilitates the production of convulsions. The entity described previously of an abnormal permeability of all cells to thiocyanate, and presumably also to chloride ions, augments this phenomenon and probably contributes to the onset of convulsions.

9. The desirable method of treating this metabolic defect is first to attempt to dehydrate the patient, thereby reducing the degree of edema as well as increasing the tonicity of the body fluid, after which saline solutions may be administered.

APPENDED REPORTS OF PATIENTS IN WHOM CONVULSIONS DEVELOPED POSTOPERATIVELY, DUE TO ABNORMALITIES OF WATER METABOLISM

CASE 1.—T. G. B., a 68 year old white man, was admitted to the University Hospital on Sept. 29, 1948, for the repair of a fecal fistula which had resulted from a perforation of a diverticulum in 1938. Because of the numerous diverticula and the presence of polyps within the colon, a total colectomy was performed, with anastomosis of the terminal portion of the ileum to the pelvic colon. The operation was performed with the patient under gas, oxygen and ether anesthesia and was tolerated well. Immediately after operation he received 5 per cent dextrose in distilled water intravenously.

On the first postoperative day generalized convulsions developed involving both arms, the legs and the face. There were no focal signs. The patient became violent, restless and unresponsive. His aimless thrashing about was controlled by intramuscular administration of paraldehyde. Physical examination revealed the pupils to be dilated, and they reacted poorly to light. Extraocular movements were normal, as were the fundi. Deep reflexes were absent in the arm and were active and equal in the knees. The Babinski sign was negative. The neck was not stiff, and heart sounds were normal. The rectal temperature remained about 99 F., the pulse rate was 90 per minute and the blood pressure was 160 mm. of mercury systolic and 90 mm. diastolic.

A diagnosis of cerebrovascular accident, probably thrombosis, was made. Because of the absence of any localizing findings, it was impossible to localize the process, but it was the impression of the neurologist that the pathologic process probably was deep seated in the region of the thalamus.

The patient's disoriented state persisted for 10 days. During this time he was incontinent and continued thrashing about. He was treated by supportive measures, consisting of intravenous administration of hypertonic glucal solutions and sedation with paraldehyde.

The blood chemical studies were of particular interest because of a severe hypochloremia which developed postoperatively. The day before surgical intervention the serum chlorides were normal (103 milliequivalents) and the carbon dioxide-combining power was normal also (21 milliequivalents). The hemoglobin content was 14.8 Gm. per 100 cc., and the total serum protein averaged 7.5 Gm. per 100 cc. of serum. The blood urea nitrogen was 11 mg. per 100 cc.

After the operation while the patient was suffering from convulsive seizures, the serum chlorides had dropped precipitously to 81 milliequivalents. Associated with the chloropenia, a large outpouring of sodium chloride in the urine developed, averaging 8.2 Gm. per liter, which resulted in a loss of 26.65 Gm. of urinary sodium chloride on the first postoperative day. The serum chloride continued to drop and reached the abnormally low value of 53 milliequivalents on

the sixth day after operative intervention. The carbon dioxide–combining power did not rise proportionally to the decrease of serum chloride. It hovered in the vicinity of 30 milliequivalents while the serum chloride was at its lowest level. The serum sodium decreased also to 108 milliequivalents, and the potassium was 2.2 milliequivalents. A slight increase in blood urea nitrogen occurred. The chloride in the urine gradually decreased and on the third postoperative day averaged 1.5 Gm. per liter. It subsequently disappeared from the urine. The urine sodium on October 3 equaled 0.6 milliequivalents and the potassium 1.5 milliequivalents.

The patient's weight did not alter greatly, which fact indicated that there was no great loss or gain of body water. Although some of the chloride loss subsequent to operation could be attributed to gastric aspiration of chloride-containing fluid, it is significant that a pronounced decrease of blood chloride occurred immediately after the operation, at which time there was no excess loss of chloride except the abnormally large quantity in the urine. The patient was last seen in May 1949 and was perfectly well.

Case 2.—A. H., a 64 year old woman, was admitted to the University Hospital on May 1, 1949, for excision of a benign adenoma of the thyroid gland. Her past history revealed that a radical mastectomy for adenocarcinoma of the breast was performed in September 1931, followed by high voltage roentgen ray therapy. She has no signs of recurrence of the breast cancer at present.

On May 6 a local excision of a solitary nodule of the left thyroid gland was accomplished with the patient under gas, oxygen and ether anesthesia. The pathological specimen revealed a benign or nontoxic adenoma.

The immediate postoperative condition was excellent, but about noon of the first postoperative day the patient became confused and unresponsive and lapsed into a semicoma. Her deep reflexes were normal, and the pulse rate, heart sound, blood pressure and temperature were also normal. Six hours after the onset of the lethargic state, generalized convulsions developed which lasted about five minutes. After cessation of the convulsive seizures, she remained disoriented and thrashed about. Three hours later she again had generalized convulsive seizures. Intravenous administration of calcium gluconate was without effect.

Physical examination revealed the pupils of the eyes to be dilated, but they responded to light and in accommodation. Extraocular movements were normal. The cranial nerves were intact, and deep reflexes were normal and equal. The abdominal reflexes were normal, and the Babinski test gave a negative reaction. Trousseau and Chvostek signs were negative.

It was the impression that the patient had suffered a cerebrovascular accident, probably in a silent area. The episode lasted approximately 18 hours, after which the patient recovered gradually and had no recollection of the entire experience.

The interesting observation was the hypochloremia which accompanied the bizarre clinical course. Before surgical intervention the serum chloride was the normal level of 107 milliequivalents, and after a relatively minor surgical procedure, which lasted about 20 minutes and in which there could not have been an abnormal loss of chloride, the serum chloride dropped to 86 millequivalents. A low carbon dioxide–combining power of 17 milliequivalents accompanied the chloropenia. Serum sodium was 141 milliequivalents and potassium 4.2 milliequivalents at this time. The blood urea nitrogen was 9 mg. per 100 cc. The patient was given 22.5 Gm. of sodium chloride intravenously as isotonic saline solution. Three days subsequent to the hypochloremia, her serum chlorides equaled 100 milliequivalents. During the convulsive seizures, the blood sugar was 138 mg. per 100 cc., which deceased to 102 mg. with clinical recovery.

On May 1 the coagulation time was three minutes and the bleeding time one and a half minutes. On May 7, during the convulsion, the coagulation time was 2 minutes 15 seconds and the bleeding time 3 minutes 15 seconds. Her white blood cell count on admission was 6,650 cells per cubic millimeter, with 67 per cent polymorphonuclear cells, 22 per cent lymphocytes, 6 per cent monocytes, 3 per cent eosinophils and 2 per cent basophils.

Immediately after the operative procedure the white blood cell count had risen to 13,700 per cubic millimeter, with 94 per cent polymorphonuclear cells, 3 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils.

The patient recovered completely, with no signs of residual disease of the central nervous system or of electrolytic abnormalities. She was discharged from the hospital on May 11, 1949, and observed in the outpatient clinic three weeks later. She was perfectly well.

CASE 3.—M. K., a 75 year old woman, was treated with high voltage roentgen ray therapy and radium for a squamous carcinoma of the vagina in February 1946. She remained well until March 1949, when loss of appetite, episodes of severe abdominal pain in the right lower quadrant and a loss of weight developed. She has had an old ununited fracture of the right femoral neck for several years for which she has refused therapy.

A diagnosis of carcinoma of the cecum was made by roentgenographic studies, and on May 24, 1949, the right side of the colon and part of the abdominal wall were resected. She remained well immediately after surgical treatment, but on the night of the first postoperative day, she showed confusion, disorientation and lethargy and resisted routine nursing care. She could not understand questions and became delirious.

Physical examination revealed the patient to be semicomatose, with flushed face and warm skin. Her blood pressure was 120/80, pulse rate 100 beats per minute and temperature 101 F. The pupils were equal and reacted to light and in accommodation. The left eye tended to deviate laterally. The tongue protruded in the midline, and no facial palsy was evident. The expansion of the right side of the chest was reduced, and numerous fine and crackling rales were audible over this region. All deep reflexes were reduced equally and bilaterally. Babinski signs were negative. It was felt that this patient was suffering from a cerebrovascular accident in a silent area. Bronchopneumonia of the right lung was diagnosed also.

Blood chemical studies performed at this time revealed chloropenia (84 milliequivalents) and a carbon dioxide–combining power of 22 milliequivalents. An increase in the blood urea nitrogen from 12 to 21 mg. per 100 cc. occurred.

The urine output of chloride during the first postoperative day averaged 4.6 Gm. of sodium chloride per liter of urine. The patient's weight increased 2.7 Kg., associated with a scant urine output during the immediate postoperative period. She was treated conservatively with 9 Gm. of sodium chloride per day and recovered gradually. On the twelfth postoperative day she was well, and while preparations were being made for her discharge she suddenly died, presumably from a cerebrovascular accident.

Postmortem examination revealed bilateral patchy atelectasis of the lungs and hydronephrosis and acute pyonephritis on the left due to ureteral stricture. The microscopic examination of the brain revealed diffuse demyelination, with a few foci of brain softening which caused microglia, fat granules and proliferative oligodendroglia surrounding centers of necrotic cerebral tissue. Cerebral arteriosclerosis was marked.

Comment.—This patient's cerebral arteriosclerosis apparently made her sensitive to alterations of tonicity, which probably produced the postoperative symptoms and abnormal blood chemical picture. A cerebral accident at the time of discharge was not compatible with life.

CASE 4.—M.H., a 74 year old woman, was admitted to the University Hospital on July 24, 1948, for surgical extirpation of a carcinoma of the rectum. Her symptoms consisted of alternating constipation and diarrhea, burning during defecation and blood and mucus in the stools. A weight loss of 40 pounds (18 Kg.) had occurred during the last year. She had no cardiovascular or cerebral symptoms except slight dyspnea and ankle edema of three years' duration. Her electrocardiogram was normal, and her blood pressure was 140/60. On July 30, 1948, a combined abdominal-perineal resection was performed which the patient tolerated well, and her immediate postoperative course was proceeding satisfactorily until the evening of the third postoperative day, when she became irrational and unresponsive. She perspired freely and thrashed her arms and legs aimlessly. Her eyes were blank and rolled about. The subsequent day she kept mumbling and went through chewing motions constantly.

Physical examination revealed an unresponsive woman mumbling incoherently. Her pulse rate was 64 beats per minute and the blood pressure 130/70. Her eyes reacted to light and in accommodation. The fundi revealed moderate arteriosclerosis. All deep reflexes were hyperactive, bilateral and spontaneous. Babinski signs were bilaterally present. Rigid resistance of the extremities to passive motions, more marked on the left, was observed. No paralysis of the extremities existed. A positive Hoffmann sign was present in the left hand. A diagnosis of cerebrovascular accident was entertained. Two days after the onset of the cerebral symptoms

she demonstrated signs of improvement. She responded to noxious stimuli, opened her eyes and appeared to recognize things. On the third day after the episode she asked intelligent questions. She continued to improve and was discharged about Aug. 15, 1948 (sixteenth postoperative day), with no residual signs of the cerebrovascular accident.

Data on the patient's blood were of particular interest. The preoperative examination revealed a hemoglobin content of 7 Gm. per 100 cc., which was corrected with whole blood transfusions. The total serum protein was 5.7 Gm. per 100 cc., with 3.8 Gm. of albumin and 1.9 Gm. of globulin. The serum chlorides were 107 milliequivalents per liter. On the day that postoperative complications developed the chloride had dropped to 91 milliequivalents, with a normal carbon dioxide–combining power of 24 milliequivalents. The serum chlorides continued to drop, and on August 4 (fifth postoperative day) they were at the low level of 66 milliequivalents and the carbon dioxide–combining power was 19 milliequivalents.

Between August 3 and 7 she was treated essentially with hypertonic glucose solution. As she recovered the serum chloride level gradually increased, and on August 10 it had risen to 88 milliequivalents and there was a normal carbon dioxide–combining power of 23.5 milliequivalents. She was discharged and was last seen on July 5, 1949, when she was entirely asymptomatic.

LIVER AS A FACTOR IN EXPERIMENTAL RENAL HYPERTENSION

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THE MOST recent theories concerning the causative factors in experimental renal hypertension and their interrelationships may be stated as follows:

1. Renin, a protein-like substance, is formed in excessive amounts by an "ischemic" or "anoxemic" renal parenchyma. Hypertensinogen, the precursor of hypertensin, is a substance of the alpha-globulin fraction of the plasma which has been demonstrated to be formed in the liver and has a specificity for reacting with renin, produced in the kidney, to form hypertensin, the vasopressor substance.

2. The existence of a hitherto undescribed homeostatic system for the regulation of the peripheral circulation has been disclosed in studies by Shorr, Zweifach and Furchgott.[1] "This system is made up of two components, one of hepatic (V. D. M.), the other of renal origin (V. E. M.). Evidence of the presence of such a circulatory homeostatic system, its mode and sites of origin, and the manner in which it regulates the behavior of the peripheral vascular bed, was first derived from studies on experimental hemorrhagic and traumatic shock. Subsequent studies have shown this homeostatic system to be likewise involved in the syndrome of renal hypertension." The most probable mechanism responsible for the formation of these vasotropic factors during the shock syndrome is, as was pointed out, the reduced oxygen tension which results from the reduction of blood flow to the liver and skeletal muscle (V. D. M.) and the kidney (V. E. M.).

Page, McSwain, Knapp and Andrus [2] found that removal of the liver in dogs causes the blood pressure in experimental renal hypertension to fall. The same result was obtained when carbon tetrachloride alcohol mixtures were administered to the animals. The results were explained on the basis of liver damage which, in turn, reduced the renin activator content of the plasma.

Since it has been demonstrated that the level of hypertensinogen in the plasma is maintained by its production in the liver and since a decrease in hypertensinogen

Aided by the Grunow Surgical Fund.

From the Department of Surgery, Northwestern University Medical School.

Read before the Section on Surgery at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 30, 1950.

1. Shorr, E.; Zweifach, B. W.; Furchgott, R. F., and Baez, S.: Hepatorenal Factors in Experimental Hypertension, in Factors Regulating Blood Pressure, Transactions of the First Conference, April 24-25, 1947, New York, Josiah Macy, Jr., Foundation.

2. Page, I. H.; McSwain, B.; Knapp, G. M., and Andrus, W. DeW.: The Origin of Renin-Activator, Am. J. Physiol. **135**:214, 1941.

is described only in some cases of experimental acute liver insufficiency,[3] we have attempted to produce low grade hepatic disease to inhibit the formation of hypertensinogen and thereby relieve an experimentally produced hypertension. Likewise, reducing the blood flow to the liver should increase the formation of the vasodepressor factor considered to play a role in the homeostatic system involved in the syndrome of experimental renal hypertension.

EXPERIMENTS

We produced experimental renal hypertension by the application of a Goldblatt clamp on one renal artery and three weeks later placing a clamp on the remaining renal artery. Direct readings of the blood pressure were taken from the femoral artery with a Tycos manometer. Sufficient time was allowed to elapse so that elevations of the blood pressure were constant before subsequent experiments were carried out. Occasionally, a figure-of-8 tape ligature was wrapped about the right kidney and the left kidney was removed according to the Grollman method of producing experimental hypertension. After each surgical procedure 300,000 units of penicillin was given to the animal.

After the elevated blood pressure was well established in four dogs a Goldblatt clamp was placed on the common hepatic artery after infiltration of the periarterial tissue with procaine solution. The hepatic plexus which surrounds the artery was carefully stripped away. This procedure avoids the vasoconstriction produced by manipulating the artery and leaves the caliber of the vessel normal. This step is essential in order to place the clamp and adjust it to obtain a uniform reduction of the lumen of the vessel. For this purpose, the screw of the Goldblatt clamp is completely tightened down and then one complete turn to release it is made. Subsequently, the liver branches of the hepatic artery were severed between double ligatures in these animals in order to obtain a complete deprivation of the arterial supply to the liver.

In two dogs with well established hypertension, the hepatic plexus was sectioned in order to determine whether or not interference with the sympathetic nerve supply would influence the course of the hypertension.

In five hypertensive dogs a Goldblatt clamp was placed on the portal vein at the entrance of the vessel into the liver and above the pancreatic vein. When it is completely open and in place, the lumen of the clamp is enough to reduce the portal vein by about one half to two thirds without producing symptoms in the animal.

Another five dogs with hypertension were operated on, and both the common hepatic artery and the portal vein were clamped, as we have described.

Prothrombin concentration in the plasma,[4] acid and alkaline phosphatase in the serum,[5] total serum proteins,[6] glucose[7] and hematocrit determinations were made before and after these procedures were carried out on the vessels.

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3. Munoz, J. M.; Braun-Menendez, E.; Fasciolo, J. C., and Leloir, L. F.: The Mechanism of Renal Hypertension, Am. J. M. Sc. **200**:608, 1940.

4. Tanturi, C. A., and Banfi, R. F.: An Improved Method for the Determination of Plasma Prothrombin, J. Lab. & Clin. Med. **31**:703, 1946.

5. Gomori, G.: Determination of Phenol in Biologic Material, J. Lab. & Clin. Med. **34**:275, 1949.

6. Mortensen, R. A.: A Rapid Method for the Determination of Serum Protein, J. Lab. & Clin. Med. **27**:693, 1942.

7. Nelson, N.: A Photometric Adaptation of the Somogyi Method for Determination of Glucose, J. Biol. Chem. **153**:375, 1944.

RESULTS

Occlusion of the common hepatic artery in these animals produced no permanent decrease in the blood pressure levels. Neither did section of the hepatic plexus affect the blood pressure. Ligation of the liver branches of the hepatic artery reduced the

TABLE 1.—*Changes in Blood Pressure Levels Produced in Hypertensive Dogs by Partial Occlusion of Hepatic Vessels*

Dog	Renal Operation	Systolic Blood Pressure, Mm.	Partial Occlusion of Liver Vessels	Blood Pressure, Mm.	Course
25H	12/30/48 left renal artery clamped 2/24/49 right kidney removed	3/10/49—184 4/ 5/49—194 5/10/49—190	5/26/49 clamp on hepatic artery; no effect on blood pressure 6/14/49 ligation of liver branches of hepatic artery	6/17/49—175 6/22/49—150 6/27/49—140 7/19/49—160 7/21/49—190 9/26/49—200	9/28/49 ligation of portal vein; portacaval shunt 9/29/49 died
35H	5/3/49 renal arteries clamped bilaterally	6/27/49—190 7/29/49—195	7/29/49 hepatic artery ligated	8/ 1/49—190 8/ 4/49—170 8/10/49—155 8/31/49—150 8/19/49—145 10/ 4/49—180	10/5/49 clamp on portal vein 10/7/49 died
22H	11/18/48 left kidney compressed by figure-of-8 ligature (Grollman method); right kidney removed	6/27/49—175	10/14/49 clamp on portal vein 12/14/49 portacaval shunt	10/20/49—130 12/ 7/49—132 1/ 4/50—133 2/ 1/50—114	2/6/50 died
51H	11/23/49 right renal artery clamped 12/7/49 left renal artery clamped	1/ 4/50—200	1/6/50 clamp on portal vein 1/18/50 portal vein completely ligated; portacaval shunt	1/17/50—210 1/23/50—190 2/ 7/50—200 2/28/50—160 3/10/50—160 3/22/50—140 4/10/50—140 4/24/50—122	Living May 1, 1950
56H	1/17/50 right renal artery clamped 2/3/50 left renal artery clamped	2/21/50—210 2/24/50—220	2/24/50 clamp on portal vein 3/31/50 closure of portal vein clamp; portacaval shunt	3/ 3/50—170 3/22/50—130 3/29/50—130 4/ 6/50—125 4/10/50—125	Living May 1, 1950
9H	5/13/48 renal arteries clamped	6/ 8/48—180	6/8/48 clamps on portal vein and common hepatic artery 12/3/48 portacaval shunt	8/31/48—130 10/10/48—140 11/10/48—130 3/10/49—120 7/29/49—120 11/15/49 died	Survived 13 mo. and 15 days
15H	7/16/48 renal arteries clamped bilaterally	7/27/48—175	8/2/48 clamps on portal vein and common hepatic artery	9/31/48—170 12/28/48—150 6/27/49—150	10/3/49 dog killed
18H	8/4/48 left kidney compressed by figure-of-8 ligature (Grollman method) 8/20/48 right kidney removed	8/31/48—180	9/9/48 clamps on portal vein and common hepatic artery 12/29/48 portacaval shunt	9/14/48—140 10/12/48— 80 11/ 9/48—120 11/23/48—110 12/28/48—102 1/10/49—102 7/10/49—100	8/23/49 died
61H	1/30/50 renal artery clamped 2/21/50 left renal artery clamped	3/21/50—215	3/21/50 clamps on portal vein and common hepatic artery	3/30/50—190 4/ 3/50—178 4/10/50—160 4/24/50—142	Living May 1, 1950

blood pressure to normal levels, but this decline was only transient and the period during which this occurred varied with each animal (table 1).

Occlusion of the portal vein produced a fall in the systemic blood pressure which persisted until the animal was killed, and in some cases this interval was as long as one year. In two animals of this group the blood pressure fall never went below 150 mm., and at reoperation the clamps were tightened, resulting in death of the animals. A well developed collateral circulation was not present in either of these animals. Later, we learned that in similar instances the portal vein flow had to be reduced gradually in stages to insure survival of the animal.

In the animals in which the common hepatic artery and the portal vein were occluded, the blood pressure was decreased in every instance and the animals lived until they were killed.

After all these procedures the dogs showed no symptoms of illness. They remained alert and ate normally although most of them lost weight. At the end of two or three months in those dogs in which a clamp was placed on the portal vein a dilatation of the veins in the abdominal wall was observed and a well developed intra-abdominal collateral circulation was present.

Changes in the blood chemistry were directly proportional in these animals to the microscopic changes demonstrable in the liver cells. Chronic mild insufficiency of the liver always followed occlusion of the portal vein, and this was reflected in the hypoprothrombinemia, hypoproteinemia and decreased hematocrit value. After

TABLE 2.—*Blood Chemical Changes in Hypertensive Dogs with Partial Occlusion of the Portal Vein*

Dog	Hematocrit, %	Glucose, Gm./ 1,000 Cc.	Proteins, Gm./ 100 Cc.	Alkaline Phosphatase, μM/Hr./Ml.	Prothrombin, %	Comment
51H						Hypertensive dog—B. P. 200
Control	48	0.79	6.57	1.24	89	1/ 6/50 clamp on portal vein
3/ 3/50	41	0.81	5.6	8.5	58	1/18/50 Eck fistula
3/27/50	40	0.76	6.2	8.1	84	3/ 3/50 B. P. 170
						3/27/50 B. P. 140
						4/24/50 B. P. 122
56H						Hypertensive dog—B. P. 220
Control	46.5	0.81	5.5	0.6	93	2/24/50 clamp on portal vein
3/ 3/50	30.4	0.90	6.0	2.8	94	3/22/50 B. P. 135
3/27/50	31.0	0.80	5.4	0.9	107.0	3/31/50 Eck fistula
						4/ 6/50 B. P. 130
P. C. 5						Normal dog
Control	52	0.80	6.0	2.0	89	1/13/50 clamp on portal vein
3/ 1/50	54.1	0.61	6.1	2.7	51.0	4/10/50 killed
P. C. 7						Normal dog
Control	57	0.79	6.2	1.22	75	1/16/50 clamp on portal vein
3/ 2/50	48	0.65	6.2	2.3	46	4/12/50 killed

ligation of the liver branches of the hepatic artery, changes in phosphatase were observed, interpreted by us as a direct result of the cholecystectomy,[8] which was a necessary step in this operation (table 2).

COMMENT

Although it is obvious that the most constant decrease in the blood pressure of dogs with experimental renal hypertension is obtained when both the common hepatic artery and the portal vein are occluded, it is apparent that the more important of the two vessels is the portal vein.

A Goldblatt clamp placed on the common hepatic artery only will not completely obliterate the arterial supply to the liver, since in the dog the common hepatic artery courses from its origin in the celiac axis posterior to the duodenum, approximately 5 to 8 cm. from the pylorus. After reaching the antimesenteric border of the

8. Drill, V. A.; Annegers, J. H., and Ivy, A. C.: Effect of Cholecystectomy on Liver Function, Proc. Soc. Exper. Biol. & Med. **54**:242, 1943. Tanturi, C. A.; Canepa, J. F.; Bay, R., and Banfi, R. F.: Experimental Study on Liver Function Tests, Surg., Gynec. & Obst. **83**:171, 1946.

duodenum, it ascends and courses in a transverse, or oblique, direction posterior to the portal vein and the common bile duct, where it terminates in the larger, posterior-superior pancreaticoduodenal artery and the small, right gastric artery. That portion of the common hepatic artery which lies posterior to the portal vein and the common bile duct forms a curve with its convex portion directed toward the hilus of the liver. The liver branches, usually four to six in number, arise from the convex portion of the artery In these experiments the clamp was placed on the artery before the liver branches were given off, so that the arterial circulation of the

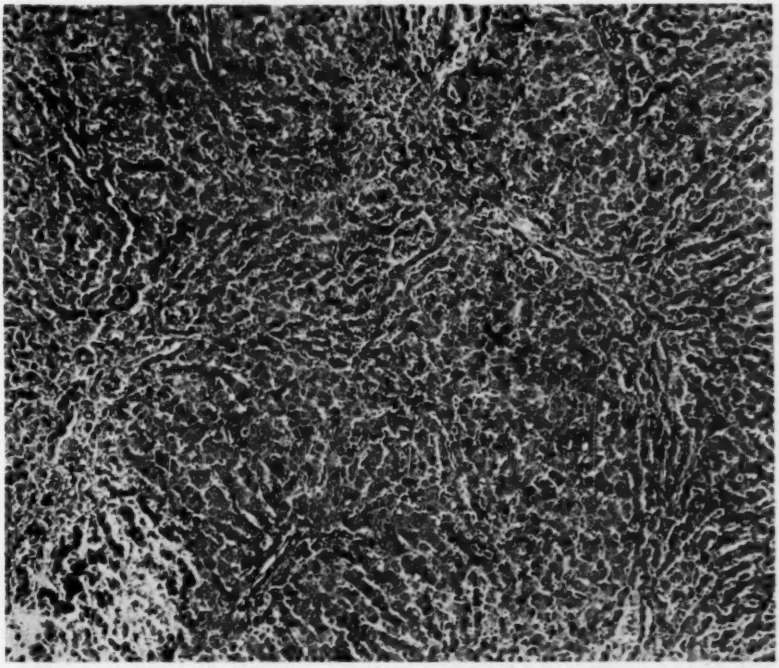

Fig. 1.—Photomicrograph of the liver of a hypertensive dog with occlusion of the hepatic arterial supply. Only a slight degree of cloudy swelling of the liver cells is present. (Hematoxylin and eosin stain; × 63.)

liver was maintained by the anastomoses between the inferior pancreaticoduodenal and right gastroepiploic and the posterior-superior pancreaticoduodenal and right gastric arteries. This will explain the lack of microscopic evidence of histological changes in the liver and the absence of blood chemical alterations in this group of animals (fig. 1).

Ligation of the liver branches of the hepatic artery in the dog is almost always followed by death, and many of the findings noted in a hepatectomized animal were observed in the moribund animals after occlusion of the entire arterial blood supply to the liver.

If penicillin is given immediately after the ligation of all the arterial blood supply to the liver, the dogs survive.[9] Markowitz, Rappaport and Scott [10] learned this same fact independently.

As can be seen in figure 2, occlusion of the entire arterial supply to the liver in hypertensive dogs produces only a temporary drop in the blood pressure, but often to normal levels. This change was always accompanied with a mild degree of liver insufficiency as shown by hypoprothrombinemia, hypoproteinemia and decreased hematocrit levels. After a variable period the blood pressure resumed its hypertensive level and the blood chemistry returned to normal. It is known that there is a reciprocal relation between the blood flow in the hepatic artery and that in the portal vein, and these changes in the blood pressure and blood chemistry may be explained by the interval of time necessary for the portal vein blood flow to compensate for the absence of the arterial blood supply.

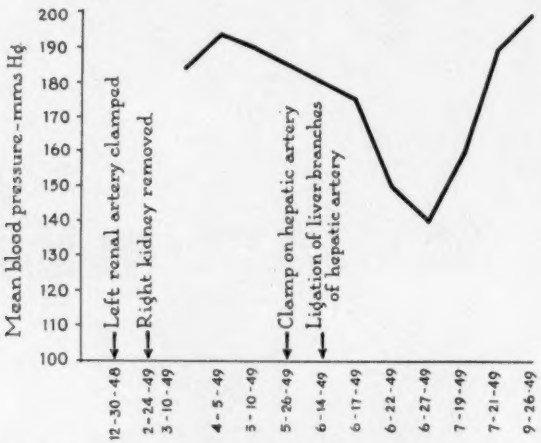

Fig. 2.—Temporary decrease in the blood pressure of a hypertensive dog (dog 25 H) following occlusion of the arterial supply to the liver.

It is well known that dogs successfully withstand partial occlusion of the portal vein, or total occlusion, if a portacaval shunt is established. It has been our experience that to obtain reduction of the blood pressure in hypertensive dogs sufficient partial occlusion of the portal vein should be reached to produce histological evidence of a mild, chronic insufficiency of the liver. This is represented microscopically by fatty infiltration of the liver cells with well preserved nuclei (fig. 3). The same changes in the liver can be obtained by total occlusion of the portal vein plus a portacaval shunt.

It has been said that an Eck fistula dog is less resistant, that an atrophy of the liver occurs and that symptoms of meat poisoning develop. We have observed

9. Davis, L.; Tanturi, C. A., and Tarkington, J.: The Effect of Reduced Blood Flow to the Liver in Renal Hypertension, Surg., Gynec. & Obst. **89**:360, 1949.

10. Markowitz, J.; Rappaport, A., and Scott, A. C.: Prevention of Liver Necrosis Following Ligation of Hepatic Artery, Proc. Soc. Exper. Biol. & Med. **70**:305, 1949.

atrophy of the liver but no other changes in our animals, perhaps because of the prophylactic administration of penicillin.

It has been our experience that when partial occlusion of the portal vein failed to reduce the blood pressure in hypertensive dogs, it was because of the disproportion between the small size of the vein and the lumen of the Goldblatt clamp. Observation of cyanosis of the intestine is not a completely reliable method of determining the efficient degree of partial occlusion of the portal vein, so that some failures in reducing the blood pressure occur. In readjusting the clamp, we have found no certain method of insuring survival of the animal. In each of

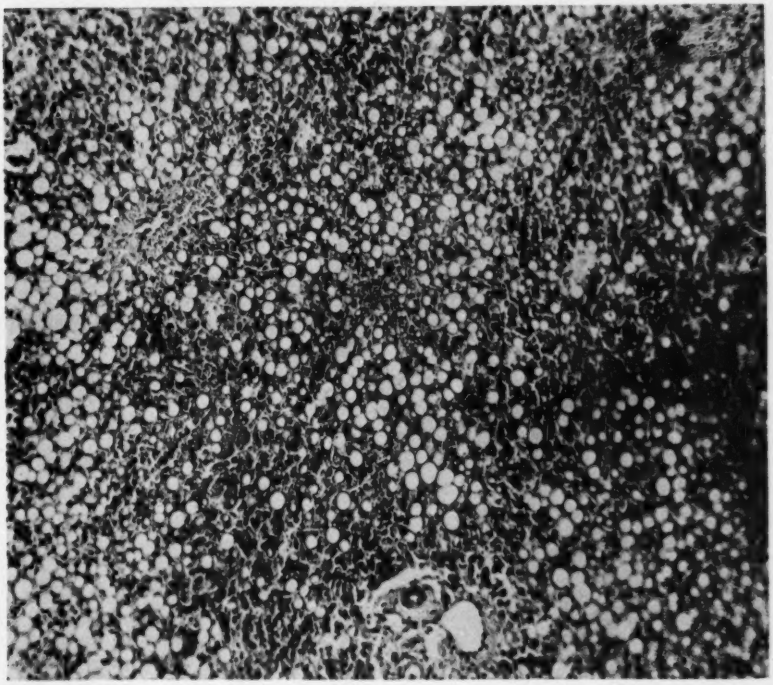

Fig. 3.—Fatty infiltration of the liver of a hypertensive dog with partial occlusion of the portal vein. The nuclei of the liver cells are preserved. (Hematoxylin and eosin stain; × 63.)

these instances we found no evidence of an intra-abdominal collateral venous circulation, and this supported our opinion that a mild insufficiency of the liver must be established in order to reduce the systemic blood pressure in the hypertensive animal.

Although the blood chemistry changes do not indicate the marked insufficiency of the liver to be expected when both the hepatic artery and the portal vein are partially occluded, the fact remains that this procedure in our experiments invariably produces a reduction in the systemic blood pressure in the hypertensive dogs (fig. 4).

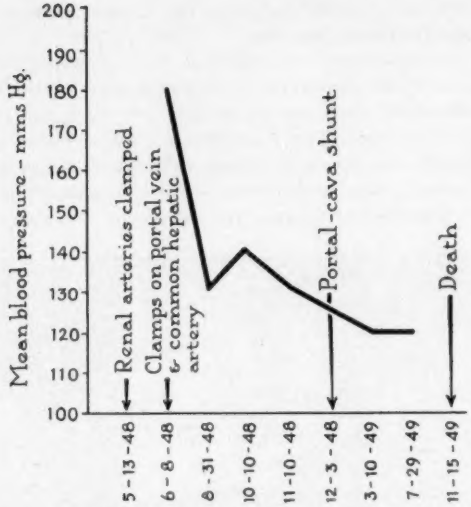

Fig. 4.—Reduction of the blood pressure of a hypertensive dog (dog 9H) following partial occlusion of the portal vein and the hepatic artery.

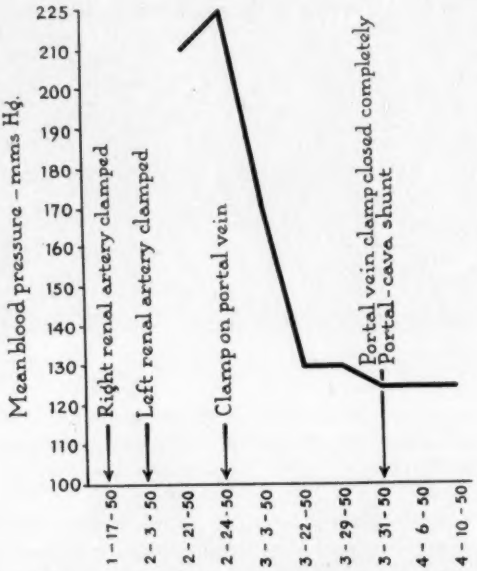

Fig. 5.—Reduction of the blood pressure of a hypertensive dog following partial occlusion of the portal vein.

To rule out the possibility that the decline in the systemic blood pressure observed in these experiments was due to an accumulation of blood in the splanchnic area, as the result of the increased portal collateral circulation, portacaval shunts were performed on the animals with partial occlusion of the portal vein and those with partial occlusion of both the portal vein and the hepatic artery. This procedure did not alter the sustained reduction of the systemic blood pressure but did improve the general condition of the animals.

In our previous report [9] we stated that portal hypertension developed after partial occlusion of the portal vein because we accepted the presence of dilated abdominal veins as a sign of portal hypertension. In these experiments we measured the pressure in the portal vein and found that a portal hypertension did not occur.

The reduction in systemic blood pressure observed in these experiments does not occur immediately after partial occlusion of the portal vein, which fact suggests an indirect, rather than a direct, participation in the mechanism controlling the systemic blood pressure (fig. 5). These results also point out that the liver plays a role in the humoral mechanism involved in experimental renal hypertension and lend support to the two current theories which have been proposed to explain the mechanism of experimental renal hypertension.

CONCLUSIONS

1. Reduction of the blood flow to the liver decreases the systemic blood pressure of dogs with an experimental renal hypertension.

2. Reduction of the blood flow in the portal vein is more effective in lowering the systemic blood pressure than total occlusion of the arterial blood supply to the liver.

3. In order to produce a decrease in the systemic blood pressure in dogs with an experimental renal hypertension, reduction of the blood flow to the liver must be sufficient to produce a fatty infiltration of the liver cells whose nuclei are well preserved. This pathological change in the liver may or may not be detected by the presently accepted tests for liver function.

ABSTRACT OF DISCUSSION

Dr. Howard C. Naffziger, San Francisco: I suppose no one who practices medicine can fail to have an interest in hypertension and its side effects. This contribution by Dr. Davis is a particularly interesting one, and is directed toward a further understanding of disturbed physiology in hypertension.

One of the most satisfying things about this report is its source. Those of us who are practicing in somewhat narrow specialties are conscious of our debt to the general surgeons, because we have to confess that most of the advances in fundamental knowledge which affect general surgery and all specialties do come from the general surgeons; so it is particularly satisfying to find someone who is in one of the highly specialized branches who presents an offering of this sort. It certainly is most commendable.

Dr. Davis has demonstrated that a reduced flow of blood in the liver in experimental hypertension of dogs is most effective in reducing hypertension when the portal vein is occluded. It would seem to me that, from the data presented by him in a limited number of animals, these experiments certainly are worthy of prosecution in a larger number. I should like to have more data on the details affecting blood pressure.

My discussion will be brief. One point is that Dr. Harry Goldblatt is listed to discuss this paper. There is no one who has done more in recent years to supply important information in

connection with hypertension. Not the least of his contributions, I believe, is that he has been directly responsible for stimulating a large proportion of all the work which has come out on this subject.

Dr. Davis's work is logical and is based on our current beliefs and theories as to the mechanism of hypertension, but we must not be blind to the fact that we do not have real proof regarding hypertension, and we do not yet even have absolute proof of the presence of renin.

The inquiry has arisen in my mind at various times: What would be the effect of a reduction of blood flow or a limitation in physiological activity of other organs, such as the pancreas and the lungs? I am sure I do not know.

Dr. Harry Goldblatt, Los Angeles: (Dr. Goldblatt was not present at the meeting but submitted this discussion.) This contribution by Dr. Davis and Dr. Tanturi is of great interest and importance because it is another link in the chain of evidence in favor of the existence of a humoral mechanism which is probably responsible for the elevation of the blood pressure, at least in the early stage of experimental renal hypertension. We have shown that a fall of blood pressure and a decrease in the hypertensinogen of the blood occur in dogs as a consequence of bilateral adrenalectomy, but not as a result of bilateral destruction of the adrenal medulla, which means that the absence of the adrenal cortex is responsible for these effects. We have also found that poisoning of the liver with chloroform produces similar effects. From these findings we have inferred that the capacity of the liver to produce hypertensinogen may be influenced in some way by the adrenal cortex. Hitherto, experiments involving interference with the circulation of the liver were always difficult because of the rapidly fatal outcome due to necrosis of the parenchyma and toxemia from the uninhibited growth of anaerobic bacilli. Now that Davis, Tanturi and Tarkington as well as Markowitz, Rappaport and Scott have shown that these untoward effects may be prevented by the administration of penicillin, this phase of the subject has been reopened. It is, therefore, not surprising that the authors of this paper have been able to observe a fall in blood pressure in hypertensive dogs as a result of a degree of hepatic ischemia sufficient to induce morphologic alterations in the parenchyma. It remains to be demonstrated, by more direct means, why this occurs and especially to determine whether the vasodepressor material (V.D.M.) of Shorr and his collaborators plays any part in this phenomenon or whether it is only the result of a lack of production of hypertensinogen. Now that hepatic ischemia, even of great degree, may be safely produced, the answer to these questions should be quickly obtained.

Dr. Loyal Davis, Chicago: I want to thank Dr. Naffziger for discussing this paper. I am sorry Dr. Goldblatt could not be here personally, but I do thank him for sending his discussion to the officers of this section.

We believe that the majority of patients with hypertension can be successfully treated medically but that there is a group of patients whose progress is so rapid that any method by which it can be curtailed is justifiable. Consequently, these patients on whom we have operated, that is, patients with the high diastolic type of hypertension, who may have a rather rapid fatal course, make it possible for us, I think, to evaluate the importance and the type of surgical procedure necessary to stay the course of this destructive disease.

TREATMENT OF HIGH INTENSITY BURNS

EVERETT IDRIS EVANS, M.D.
RICHMOND, VA.

THERMAL injury can be induced slowly or rapidly, depending on the intensity of the source. In peacetime, most burns result from exposure to low temperatures acting over a relatively long time; thus burns from hot water or steam are inflicted at temperatures ranging from 60 to 120 C. over periods of approximately a minute down to only a few seconds. Secondary burns from actual flame are usually deep because the temperature is high (300 to 400 C.) and in most instances the exposure time has been at least several seconds.

In modern warfare when certain high explosives burst within a confined space, as on naval vessels, and especially with the explosion of atomic bombs, temperatures of exceedingly high order are achieved, so that a new type of thermal injury, the "flash burn," is made possible. An atomic bomb explosion releases enormous quantities of energy as blast, radiation (gamma and neutron) and ordinary heat. Competent observers estimate that at Hiroshima and Nagasaki (fig. 1) probably 50 per cent of the casualties were due to thermal injury (burns); so the problem of the treatment of high intensity burns has assumed major importance in atomic warfare. Fortunately, medical knowledge which will improve treatment of thermal injury inflicted by atomic explosion is equally beneficial in peacetime. In many large urban centers patients with burns caused in the ordinary manner (hot water and fires) constitute a heavy load on hospital surgical services, and throughout the world thermal injury is a common cause of death by accident.

It remains to be shown in what manner the "flash burn" of atomic explosion differs from the ordinary burn. Pearse,[1] after careful studies on pigs burned by explosion of magnesium (which under standard conditions had a flash duration period of approximately ⅓ second), is of the opinion that in this particular experimental animal the "flash burn" differs in certain characteristics from the ordinary low temperature burn. This "flash burn" was demarcated sharply from adjacent

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These studies were carried out under a grant from the Office of the Surgeon General, Department of the Army.

Read before the Section on Miscellaneous Topics at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 28, 1950.

From the Department of Surgery: Professor of Surgery and Director, Surgical Research Laboratories, Medical College of Virginia; Chairman, Subcommittee on Burns, and Member, Committee on Surgery and Committee on Atomic Casualties, National Research Council; Surgical Consultant, Atomic Bomb Casualty Commission (Far East Command), Tokyo, Japan.

1. Pearse, H. E.; Payne, J. T., and Hogg, L.: Ann. Surg. **130**:774, 1949.

normal unburned skin and in general healed in a manner somewhat different from ordinary burns.

Recently my colleagues and I have had the opportunity to study two human patients burned as a result of the accidental explosion, at a close range, of quantities of magnesium of the order studied by Pearse. The burns involved the hands and forearms. Shortly after the explosion blisters formed on the burned fingers and palms. The subsequent clinical course (the closed pressure dressing was used) of these two patients was in every way similar to that noted with ordinary burns; so we are inclined to believe that our continuing experience in the planned study and care of a fairly large number of ordinary burn patients will prove valuable in the management of thermal injury associated with atomic bomb explosions, should that disaster ever befall our civilian and military population.

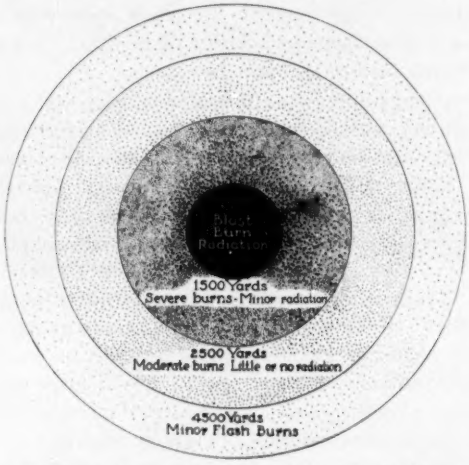

Fig. 1.—Diagram illustrating the relation of thermal injury to distance from the hypocenter in an atomic bomb burst (Hiroshima type). Immediately surrounding the hypocenter, combined injury from blast, burn and radiation is so severe that little chance for survival exists. However, in the 1,500 to 4,500 yard zone attenuation of radiation flux is so great that it is likely that little radiation damage results in this zone. The closer a person is to the hypocenter the more likely will he be to suffer severe burns. In the periphery only burns of exposed surfaces (hands and face) should be encountered.

During the past 12 months we have admitted to the Surgical Service of the Medical College of Virginia 124 patients suffering from severe burns and have treated as outpatients 574 less severely burned patients. Special burn wards, special nurses and a team of competent investigators have made it possible to make careful observations on these patients from their entry to the hospital to the time of discharge. From this experience, we want in this paper to project our opinion as to how best to plan for the care of the thousands of burn casualties that might be encountered after an atomic bomb explosion on an average American city of, say, 250,000 population. In our approach to the problem (fig. 1) every effort has been

made to search for simple methods of therapy that could be applied to mass burn casualties and to avoid complicated methods of treatment requiring large numbers of personnel, highly trained or untrained.

EMERGENCY PHASE OF BURN MANAGEMENT

If we can judge correctly from the Hiroshima and Nagasaki experience, outside the 1,500 to 2,000 yard zone from the hypocenter of an atomic bomb airburst, the "flash burn" will affect only the uncovered portions of the body, i. e., face and

Fig. 2.—Photograph of 61 year old man burned as result of gas explosion in house, with instantaneous blast and no secondary fires. Burns are present only on exposed surfaces of hands and face. Photograph taken on fourteenth day at time of grafting. This type of burn is similar to those seen in outer zones at Hiroshima.

hands (fig. 2) unless other portions of the body are burned secondarily from clothing igniting spontaneously or catching fire during escape from burning buildings. The burns may be superficial or deep, but in any case from present knowledge the treatment should be the same no matter what their depth or extent.

There are three important aspects of the emergency management of a severe burn: (*a*) prevention and treatment of burn shock, (*b*) the emergency dressing of the burn wound and (*c*) the provision of proper amounts of fluid and electrolytes to ensure adequate urine output.

PREVENTION AND TREATMENT OF BURN SHOCK (FIG. 3)

Most observers agree that the essential immediate cause of burn shock is depletion of blood volume by loss of plasma and red blood cells into the burned skin, the "zone of injury." It is also generally agreed that the larger the burn surface involved the greater the danger of burn shock. In our experience the one exception to this general rule is that although the face and buttocks occupy only a small portion of the total body surface shock can follow burns of only these areas. Vascularity of the face and buttocks is so rich that capillary damage from burns in these areas allows the local loss of plasma in amounts large enough to cause shock.

In the handling of mass burn casualties, supplies of blood and plasma may be so limited that plasma substitutes may have to be used to prevent and treat burn shock. The available plasma substitutes are gelatin and dextran; oxypolygelatin has been produced in only limited amounts and so far has received inadequate clinical trial to allow judgment of its merits as a plasma substitute. Gelatin in our

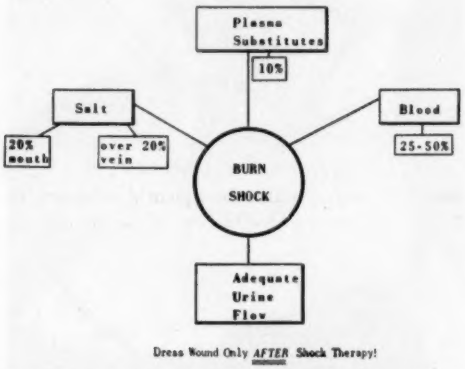

Fig. 3.—Chart illustrating more important phases of the shock problem in mass burn care. Shock must be suspected with burns involving more than 10 per cent of body surface, and it is likely that plasma substitutes will be highly effective. In burns involving 25 to 50 per cent of body surface, shock is severe and of a nature requiring some whole blood. Fluid and salt requirements can be met with oral therapy when body surface burn is less than 20 per cent. In the extensive burn (over 20 per cent) salt and water must be given by vein. An adequate hourly urine flow is a reliable index of burn shock therapy.

experience [2] is a safe and effective plasma substitute, but we believe firmly that the high viscosity of the presently available solutions of gelatin of the proper molecular size disqualify it for consideration in the treatment of mass casualties. Dextran [3] has been employed rather extensively in Sweden by Thorsen [4] and Rosenqvist [5] and by Bull and others in England [6] for burn shock therapy. Our

2. Evans, E. I., and Royal, H. S.: Ann. Surg. **121**:478, 1945.

3. Ingelman, B.: Acta chir. Scandinav. **1**:731, 1947.

4. Thorsen, G.: Lancet **1**:132, 1949.

5. Rosenqvist, H.: Acta chir. Scandinav. (Supp. 124) **95**:1, 1947.

6. Bull, J. P.; Ricketts, C.; Squire, J. R.; Maycock, W.; Spooner, S. J. L.; Mollison, P. L., and Paterson, J. C. S.: Lancet **1**:134, 1949.

limited trial of dextran (16 burn patients) indicates that it is effective for the treatment of burn shock, but we still are not satisfied that adequate renal and liver studies are available to prove its complete safety.

What burn patients will need intravenous colloid therapy, and what amounts are required to prevent burn shock? Many formulas have been developed to aid in the estimation of plasma or whole blood requirements. The hematocrit formula of 100 cc. plasma for each point rise of hematocrit over 45 per cent (i. e., hematocrit of 50 equals 500 cc. of plasma required) is helpful, but it is our conviction that insufficient workers will be available for any laboratory studies after atomic attacks. Therefore, we have been trying to judge the validity of the clinical rule of giving 1 cc. of plasma per kilogram of body weight (plasma substitutes or whole blood) for each per cent of body surface burned during the first 24 hours. Half this amount is given the second 24 hours. Except in rare instances, colloid solutions for shock therapy have not been required after the second day. When the burn surface is greater than 25 per cent, we usually give whole blood and plasma in equal quantities, regardless of the hematocrit values. In most instances, the major portion of the calculated whole blood and/or plasma required is given in the first 12 to 16 hours. The amounts of colloid indicated above seem to have prevented burn shock in our patients.

THE EMERGENCY DRESSING

Results in burn therapy have improved greatly since the general adoption of the occlusive pressure dressing, changed infrequently, following its introduction by Allen and Koch [7] in 1942. The chief difficulty in the application of this dressing in the care of mass burns would be that the method is time consuming and requires relatively well trained personnel. This has led Harvey Allen [8] and our group to investigate the advantages of a single one piece large burn dressing for extensive burns (fig. 4). Our initial studies indicate that this dressing will be highly useful, can be applied by trained lay persons in about one sixth to one tenth of the time required for the ordinary pressure dressing and will probably give satisfactory results. It is especially useful for dressing the thorax and abdomen (fig. 5). Further trial in a large series of burn patients should make it possible to reach a decision of the value of a single dressing to be used for all burns of the extremities and body.

The "flash burn" affects chiefly the exposed, unclothed surfaces, i. e., the face and hands (fig. 2). Efforts are being continued to find a simple glovelike dressing for burns of the hand. Fortunately, unless deep, most face burns heal relatively rapidly, and best without dressings, under a covering of any oil applied to allay pain. (Facial disfigurement such as ectropion is common after deep burns and requires early plastic surgery to correct the deformity.)

Wallace [9] has reintroduced the "exposure method" for the treatment of extensive burns, and some have intimated that this may be an ideal method for the care of

7. Allen, H. S., and Koch, S. L.: Surg., Gynec. & Obst. **74**:914, 1942.

8. Allen, H. S.: Personal communication to the author.

9. Wallace, A. B.: Ann. Roy. Coll. Surgeons England **5**:283, 1949.

large numbers of burn casualties. It remains to be shown how effective this method is for deep extensive burns, whether there is a saving of personnel and expense and if the method is safe for use during a period when relative chaos may prevail, such as after atomic attack. (The method obviously requires hospitalization and immobilization of the burned patient.)

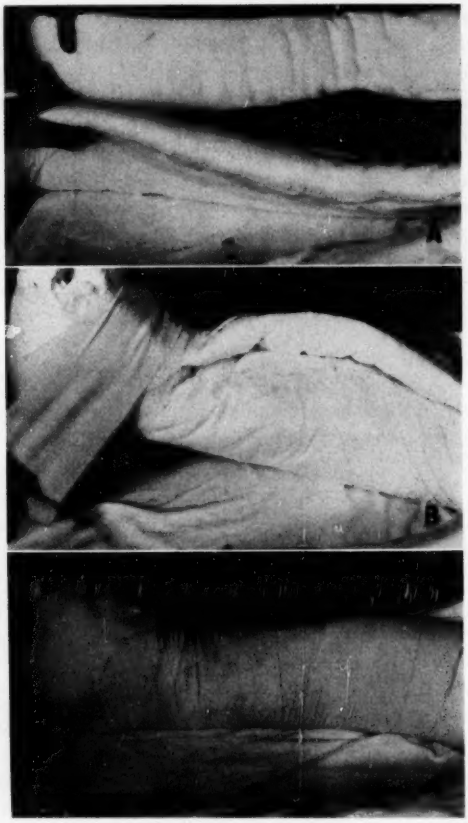

Fig. 4.—Large single type burn dressing. *A*, a burned leg is being enclosed with the single type dressing, with no ointment applied next to skin; *B*, pressure applied by use of 8 inch (20 cm.) crepe bandage; *C*, completion of occlusive pressure dressing to whole lower limb; time involved, approximately six minutes. We are currently trying out single type burn dressings of two sizes: for the lower limb or thorax and abdomen, 45 by 34 inches (114 by 86 cm.); for the upper extremities, 34 by 19 inches (86 by 48 cm.). The inner surface is fine mesh gauze and the outer closely woven cotton gauze with a 2 inch (5 cm.) layer of cotton and compressed cellulose.

One of the trying questions concerned with the emergency dressing for mass casualties is the relative efficiency of an antibiotic incorporated in the dressing, next

to the burn surface, compared with systemic antibiotic therapy. Four groups (Colebrook and others,[10] Allen and his colleagues,[11] Gurd and others [12] and Evans and Hoover [13]) apparently achieved relative success in combating infection in the burn wound by the local use (in an oil base) of a sulfonamide and/or penicillin, but this practice generally has been frowned on. After consideration of the remarkable saving of time, personnel and equipment, if local antibiotic therapy for mass burns should prove on adequate trial to be as effective as continued, repeated systemic antibiotic therapy, it would seem important that such trials again be made (see Colebrook [14]).

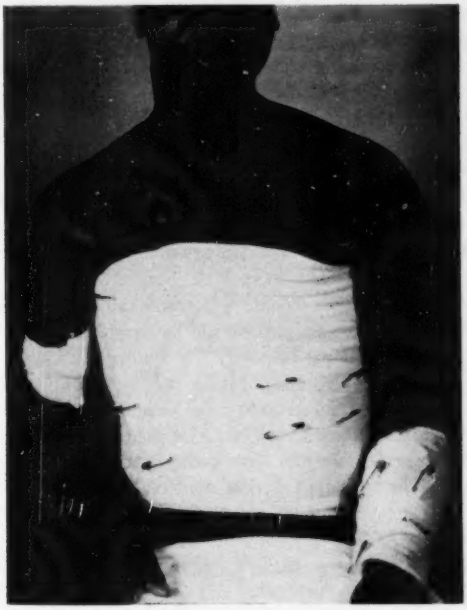

Fig. 5.—Single type pressure occlusive dressing enclosing thorax completely and upper part of abdomen, applied in same manner as that in figure 4. Time of dressing, approximately eight minutes.

10. Colebrook, L.; Gibson, T.; Todd, J. P.; Clark, A. M.; Brown, A., and Anderson, A. B.: A Study of Some Organic Arsenical Compounds with a View to Their Use in Certain Streptococcal Infections, Special Report Series 249, Medical Research Council, London, 1944.

11. Allen, J. G.; Owens, F. M., Jr.; Evans, B. H., and Dragstedt, L. R.: Sulfathiazole Ointment in Treatment of Burns, Arch. Surg. **44**:819 (May) 1942.

12. Gurd, F.; Ackman, D., and others: Technique in Trauma: Planned Timing in the Treatment of Wounds Including Burns, Philadelphia, J. B. Lippincott Company, 1944.

13. Evans, E. I., and Hoover, M. J.: Surg., Gynec. & Obst. **77**:367, 1943.

14. Colebrook, L.: A New Approach to the Treatment of Burns and Scalds, London, Fine Technical Publications, 1950, p. 109.

FLUID AND ELECTROLYTE REQUIREMENTS [15]

The most critical period for proper fluid and electrolyte replacement in the severely burned patient is the first 48 hours. After experimenting with several published formulas for estimating requirements, we now believe that they are met if the patient is given 1 cc. of electrolyte solution (0.9 per cent sodium chloride NaCl) per kilogram for each per cent of body surface burned, i. e., the same amount of electrolyte solutions as colloid (plasma, plasma substitute, whole blood) during the first 24 hours. Half this amount is given the second 24 hours.[15]

To all adult burned patients 2,000 cc. of 5 per cent dextrose in water is given daily to maintain a urine output of at least 50 cc. per hour. On admission, an indwelling polyethylene tube is placed in an external saphenous vein for this fluid therapy, and fluids are given slowly or rapidly as may be required. If the output drops below 25 cc. per hour (adult), we take this to mean that shock is impending, so more colloid solution is given rapidly.

It is recognized, of course, that should patients be able to take large amounts of fluids by mouth it may not be necessary to continue intravenous infusions of salt and water. In our experience, however, it has proved safer and easier to maintain fluid and salt balance in the burned patient during the first few days by a constant intravenous drip, kept running through the saphenous vein. Great care must be taken that the continuous infusions are given slowly, lest water intoxication result.

It should be emphasized that colloid, water and salt therapy during the first 48 hour critical period is best guided in the main by careful recording of hourly urine output by means of an indwelling catheter. In this we are in firm agreement with Cope and Moore.[16] The chief complicating factors in fluid therapy in burned patients is that if they are undertreated renal damage follows and, conversely, if overtreated, pulmonary edema may result. In patients who have suffered direct pulmonary damage, our best results have come from giving only enough fluid to maintain an hourly urinary output during the first two days of about 25 cc.

LIVER DAMAGE IN SEVERE BURNS

It has been known for many years [17] that severe damage to the liver may be associated with burns; the importance of this fact has been somewhat obscured by the recognition that tannic acid is a hepatotoxic agent. We continue to find

15. As a clinical example, a 70 Kg. man with a 35 per cent body surface burn would require the following during the first 24 hours:

plasma, plasma substitute or whole blood	$=70\times35\times1$ cc.$=2{,}450$ cc.
electrolyte solutions (0.9% NaCl)	$=70\times35\times1$ cc.$=2{,}450$ cc.
5% glucose in water	$=2{,}000$ cc.
	6,900 cc.

Half this amount of plasma and/or whole blood and electrolyte and the same amount (2,000 cc.) of 5 per cent dextrose in water is given the second 24 hours. Calculation will show that should the burn involve 60 to 75 per cent of body surface, large amounts of colloid and saline would be required if this formula were employed. Nevertheless, we rarely give more than 4,000 cc. of colloid or 4,000 cc. of saline solution in 24 hours, no matter how extensive the burns.

16. Cope, O., and Moore, F. D.: Ann. Surg. **126**:1010, 1947.

17. Bardeen, C. R.: Johns Hopkins Hosp. Rep. **7**:137, 1898

moderate to severe hepatic damage in many of our burned patients not treated with tannic acid, laboratory evidence (urinary urobilinogen, thymol turbidity, prothrombin index, sulfobromophthalein retention) of this damage showing up as early as the third or fourth day.[18] For this reason, we believe that search should be made for measures to prevent rather than treat this damage to the liver in the severely burned patient.

SUBSEQUENT CARE OF THE BURN PATIENT

In a consideration of the subsequent care of mass burns, four problems are of chief interest. (*a*) prevention and treatment of anemia; (*b*) proper employment of oral feeding for adequate nutrition; (*c*) early plastic surgery; in the main, simple covering of areas of full thickness skin loss, and (*d*) rehabilitation of the patient.

A. *Prevention and Treatment of Burn Anemia.*—Anemia can be prevented in the severely burned by the administration of some whole blood during the shock phase.[19] This we have not hesitated to carry out even in the presence of hemoconcentration, because blood volume studies with tagged red cells have shown that the peripheral hematocrit value may give a false impression of the extent of the hemoconcentration.[20]

Other laboratory studies [21] on severely burned patients indicate that throughout the course of therapy for a severely burned patient whole blood must be given as often as once weekly in amounts sufficient to maintain blood hemoglobin levels at 14 to 15 Gm. Whole blood is given at each skin grafting operation.

Severe infection promotes loss of plasma from the burn surface and appears to affect adversely the formation of new blood elements, so every effort (antibiotics, good wound care,[22] early wound covering by skin grafting) should be made to minimize infection.

B. *Oral Feeding of the Burn Patient.*—The successful operation of any intelligent surgical nutrition program for the burn patient depends largely on the emphasis placed on the proper employment of oral feedings of a diet complete in protein, fat, carbohydrate and vitamins and adequate in calories. In 1944 to 1948 we gave supplemental oral feedings, sometimes by tube, starting on the fourth or fifth day. The diet was made up as follows: 150 Gm. of dehydrated beef and liver protein mixture, 150 Gm. of powdered milk, 50 to 100 Gm. of corn oil, 150 Gm. of sucrose, 150 Gm. of dextri-maltose,* 35 Gm. of chocolate and 1,000 cc. of water (plus vitamins, especially A, B, C, D, and iron).[23] This allowed a total intake of at least 3,000 calories for each 24 hour period. This diet supported admirably the nutrition of the severely burned patient; it was possible in certain patients to continue these supplemental feedings as long as four to six months. It was admitted, however, that this particular mixture was not especially palatable

18. James, G. W., III; Purnell, O. J., and Evans, E. I.: To be published.

19. Evans, E. I., and Bigger, I. A.: Ann. Surg. **122**:693, 1945.

20. Salzberg, A., and Evans, E. I.: Ann. Surg. **132**:746, 1950.

21. James, G. W., III; Purnell, O. J., and Evans, E. I.: To be published.

22. It may be argued that the scheme for good wound care advocated by Bourdillon and Colebrook (Lancet **1**:509 and 601, 1946) is too complicated for execution after atomic attacks, but certainly any attempt to approach at least the standard set by Colebrook will result in a tremendous reduction of burn wound infection.

23. Spence, H. Y.; Evans, E. I., and Forbes, J. C.: Ann. Surg. **124**:131, 1946.

and was often taken (after persuasion) as medicine and not as food. For this reason, our dietitians under Dr. Stanley Levenson's direction have sought for a more palatable and equally nutritious oral feeding mixture. The accompanying table illustrates the composition of the basic feeding mixtures which Drs. Purnell and Rice and I have successfully used for the last two years.

In general, in the severely burned patients we have resorted to feeding through an indwelling gastric rubber tube introduced through the nostril (feeding no. 1) begun on about the fourth day. Gradually the protein and carbohydrate content of the mixture is increased so that feeding no. 6 is being used by the end of the second week. Cramps and diarrhea have been noted only rarely in patients on this regimen, and we have been gratified to see that certain badly burned patients

Tube Feedings Used at the Medical College of Virginia for Burn Patients (High Protein, High Caloric, Low Fat)

		(Increasing amounts of protein and calories)					
Ingredients		No. 1	No. 2	No. 3	No. 4	No. 5	No. 6
Eggs	.....	1	1	1	1	1	1
Skim milk powder	Gm.	225	275	380	500	550	610
Valprota (Valentine Co., Inc.)	Gm.	50	100	125	150	200	250
Evaporated milk	cc.	500	500	500	400	400	350
Karo ® (blue label)	cc.	180	220	170	90	50	60
Aquasol A	qtts.	6	6	6	6	6	6
Drisxol ®	qtts.	3	3	3	3	3	3
Methionine	Gm.	3	3	3	3	3	3
Ascorbic acid	mg.	1,000	1,000	1,000	1,000	1,000	1,000
Nicotinic acid	mg.	300	300	300	300	300	300
Riboflavin	mg.	20	20	20	20	20	20
Thiamine chloride	mg.	20	20	20	20	20	20
Syrup of pantabee ®	cc.	8	8	8	8	8	8
Sodium chloride	Gm.	3	3	3	3	3	3
Water, q. s.	cc.	3,000	3,000	3,000	3,000	3,000	3,000
Composition							
Protein	Gm.	152	200	253	303	351	400
Fat	Gm.	50	53	55	50	53	52
Carbohydrate	Gm.	313	382	405	404	414	450
Calories	.....	2,300	2,800	3,125	3,275	3,550	3,900
Sodium	.....	3.2	3.5	3.8	4.0	4.1	4.4
Volume	.....	3,000	3,000	3,000	3,000	3,000	3,000

have left the hospital after two or three months showing an actual gain in weight rather than the usual weight loss seen in patients who were permitted to eat only what they would.

Oral feedings, composed of inexpensive, easily available and properly constituted food materials remain the chief support of our surgical nutrition program for the burn patient. Supplemental parenteral administration of amino acids or of digested beef plasma protein has only rarely been needed to maintain good nutrition. Study of the excellent nitrogen balance experiments being conducted here by Dr. Stanley Levenson [24] convinces me that oral feeding regimens must be included in any plans for the care of mass casualties in atomic warfare.

C. *Early Plastic Surgery.*—The occlusive pressure dressing applied during the emergency treatment of the burned patient is generally left untouched for 10 to 14 days and then changed only under operating room conditions. Superficial burns, even if extensive, heal usually by that time, but if healing is incomplete at the first

24. Levenson, S. L.: Personal communication to the author.

dressing, a second occlusive dressing is applied, to be removed seven to eight days later. If by around the twenty-eighth day it is evident the burn will not heal except by grafting, this is done.

If it is obvious at the first dressing (10 to 14 days) of certain deep burns, especially of the hands, arms and legs, that grafting will have to be done, the immediate problem may be removal of burn slough. This is generally a slow process if it is left to nature, so efforts are being made to utilize certain chemical and enzymatic agents to hurry along the separation of the burn slough. Pyruvic acid,[25] streptokinase–streptodornase [26] and collagenase [27] prepared from Welch bacillus cultures are being applied to this type of burn wound to shorten the time for removal of burn slough and to expedite covering by skin graft.

The great majority of burn patients who require plastic surgery need only simple wound covering with split thickness grafts. With the Padgett dermatome and other mechanical devices, almost any surgeon can learn to cut skin grafts of the proper thickness, but a certain experience and nicety of clinical judgment are required in applying these simple methods to some severely burned patients. If donor sites do not heal because the graft was too thick or the patient's nutrition would not support epithelial growth in the donor site, the whole system of "early grafting" collapses.

D. *Physical Measures in the Treatment of Severe Burns.*—In the treatment of the severely burned patient who requires prolonged hospitalization, it is important that thought be given from the beginning to physical measures which can help prevent contracture of scar tissue and joints (adjacent joints as well as those directly involved), maceration of normal skin, atrophy (from disuse) and deterioration of cardiovascular and respiratory functions. Measures to prevent these effects should be instituted on the day of the patient's admission to the hospital. To avoid maceration of skin which will probably be needed later as donor sites the patient's position in bed should be changed often. A footboard to prevent foot drop is standard equipment for any patient requiring prolonged bed rest. Repeated pushing against the footboard may help preserve postural reflexes. If the patient can cooperate, daily active motion will maintain function and prevent contractures. When the pressure dressing extends over the whole hand, he must be encouraged to move the fingers inside the dressing. In most burn patients "protective splinting" develops very early, which will result in joint contractures unless a constructive effort is made to teach the patient relaxation in the initial stage. If the patient cannot cooperate, passive motion should be instituted. In the later stages, both for healed burn and grafted areas, treatments consisting of hydrotherapy or paraffin bath, massage directed toward keeping the skin mobile over the underlying structures and graded active exercises are helpful in restoring function.

Passive tilting in the early stage, such as the oscillating bed offers, is felt to be a good adjuvant to the surgical treatment of the severely burned patient. If an oscillating bed is not available, a fracture board with a footboard attached can be substituted. By means of an overhead pulley, the head of the fracture board can

25. Connor, G. J., and Harvey, S. L.: Ann. Surg. **124**:800, 1946.

26. Tillett, W. J.; Sherry, S.; Christensen, L. R.; Johnson, A. J., and Hazlehurst, G.: Ann. Surg. **131**:12, 1950.

27. Altemeir, W. L., and MacLennan, J.: Personal communication to the author.

be elevated for 10 to 30 minute periods, depending on the patient's condition. When the latter method is used, the patient should be encouraged to keep moving while in the tilted position by alternately flexing and extending the ankles and knees. The foot-down position on the oscillating bed probably evokes slight muscular contraction in the body, which in turn may result in an increased blood flow. Some [28] think that this practice may decrease the intensity of the catabolic response to injury.

When the danger of shock has passed, a graded program of general body exercises in bed will improve cardiovascular and respiratory functions and prepare the patient for ambulation.

THE BURN PROBLEM IN ATOMIC WARFARE

From the preceding paragraphs it will be plain that the care of even a few severely burned patients can be complicated and requires trained personnel, many supplies, much time and considerable patience. A fertile imagination is not required to perceive how vast, how complex and how discouraging this care could be after an atomic attack. It may be well here to list some of the burn problems for which there are as yet no answers.

(*a*) *The "Exposure Method."*—How much proper housing is required, and how simple can this be, if the exposure method could be safely adopted for the care of mass burn casualties? Will this type of care allow transport of burn patients? Can cross infection be prevented? How can immobilization of burned hands be affected? Does such immobilization lead to permanent stiffness of fingers?

(*b*) *Emergency Dressings.*—Admitting that the single, large dressing is feasible for limb and trunk burns, is the ace bandage suitable for immobilization, can these bandages be applied rapidly enough, and will they stay in place if the patient is transported? Must some form of grease ointment be placed next to the burn wound or would dry dressings suffice?

(*c*) *Infection.*—Should serious consideration be given to special trauma and burn units in casualty centers equipped with dressing stations supplied with relatively sterile washed air, according to the concept of Colebrook? [29] What is the value of locally applied antibiotics? Which is the superior antibiotic for the mixed infection commonly noted in burns—penicillin, aureomycin, chloromycetin® or terramycin? Are the sulfonamides of no use?

(*d*) *Blood, Plasma and Plasma Substitutes.*—The most pertinent question here centers around standardized collection and transfusion equipment. A bottle of blood taken in New York may have to be rapidly transported to Europe or closeby to Philadelphia. Must it be transferred to a second bottle before administration to the stricken patient? Will any adequate answer to all these questions be forthcoming unless a national blood program is activated without delay?

(*e*) *Personnel.*—We have learned, as have others, that many severely burned patients can be saved only by a group of trained persons who know how to treat shock, provide adequate nursing service, and prepare suitable oral feedings and who

28. Whedon, G. D.; Dietrick, J. E., and Shorr, E.: Am. J. Med. **6**:684, 1949.

29. Colebrook, L.: A New Approach to Burns and Scalds, London, Fine Technical Publication, 1950, pp 68-88.

know when and how to cover a burn wound with a proper graft. It is obvious that adequate care of mass burn casualties requires a host of trained and energetic persons endowed by nature with a willingness to work, often at unpleasant tasks.

COMMENT

Obviously the medical profession is confronted with a gigantic, complex task in planning for such care. Lest we be overwhelmed and thrown into despair at the magnitude of the problem, search for the best methods in the most adequately equipped hospital centers should be pushed forward rapidly. These studies must encompass the fundamental as well as applied surgical science of burns. Fortunately, the military services [30] have recognized for some time the need for this knowledge, so that active studies in the burn field are in progress even now in many hospitals

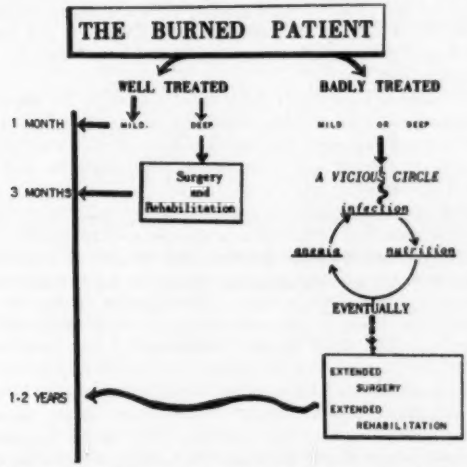

Fig. 6.—Chart illustrating difference in time involved in recovery of a well treated and a badly treated burned patient. If badly treated from the beginning, a vicious circle of infection, malnutrition and anemia results, so that whereas a well treated seriously burned patient leaves the hospital in approximately three months, the badly burned patient in whom anemia and infection develop may require one to two years' hospitalization.

and laboratories. Soon it should be possible to translate them into the practical experience of atomic defense planning.

Dismal and melancholic as the outlook for the proper care of mass burn casualties could be, there is a bright side to the picture. When the collective experience of current burn research is forged into working practice, along simple lines, civilian and military defense planning can provide adequate care for the victims of atomic attack. Atomic warfare is madness, but proper planning can separate fear from that madness, if as a nation we "maintain the serenity of real bravery and the balancing sanity of high confidence." The well treated burn patient (fig. 6), fore-

30. Considerable burn research, under support of the Medical Research and Development Board, Department of the Army, Colonel William S. Stone, Chairman, is currently in progress in hospitals and universities in this country.

warned and disciplined, can view his fate with equanimity, knowing that an alerted medical science providing satisfactory burn care will have him back at his daily work in short order. Our present task as doctors and citizens is to see to it that the nation is alerted to the atomic burn problem.

Unstinted aid and cooperation were given by our group engaged in burn investigation: Drs. O. J. Purnell and M. E. Rice, assistant resident surgeons; Dr. William T. Ham, Jr., physicist; Dr. G. Watson James, III, hematologist; Dr. Stanley M. Levenson, surgical nutrition; Dr. Lynn Abbott, biochemist; Miss Edith Vail, physical medicine. Their continued efforts and encouragement have made possible these studies on the burn problem.

ABSTRACT OF DISCUSSSION

Dr. James Barrett Brown: The skin grafting of deep burns was a major portion of the work in Plastic Surgery Centers in World War II, and possibly a greater amount of such work will be required in the next war. In the medical department history of World War I no report is included on burns and free skin grafting is mentioned only in part of one sentence. At one time during World War II the Plastic Surgery Centers in the Zone of Interior had 11,000 patients needing 33,0000 operations, so that the problem of the repair of burns may be seen to be one of great magnitude.

Severely burned patients were received by these centers in all degrees of debilitation, chronic shock, infection and pain. A basic philosophy was used of getting the wounds clean as soon as possible and restoring what skin had been lost. In this detail, kindness, painstaking work, gentleness and all possible use of antibiotics were employed, plus the correction of blood and nutritional deficiencies.

Patients improved as the wounds were closed, either by spontaneous healing or grafting, and grafting was often lifesaving. Grafting was done as soon as possible, many times within three weeks, but with patients evacuated as much as 8,000 miles this was frequently delayed. As to immediate excision and grafting ot burns, this is not recommended in military practice nor in any practice except in isolated instances. There are no figures that will bear analysis in favor of widespread immediate excision and grafting of large deep burns. To employ this practice on a large scale by central direction would cause damage more than it would do good.

Observation of the condition of severe burns on the patients' arrival at Plastic Surgery Centers confirmed all data previously studied and reported. If the wounds could be kept free of chemical, traumatic, and bacterial irritation, they were in the best condition. For this, the use of fine 44 mesh greased (petroleum jelly) gauze next to the wound with a firm waste pressure fixation dressing resulted in the best wounds. If irritations did occur, and they most often did from unchanged dressings, then areas of burn that were originally second degree were so heavily infected by pus that they were changed into full thickness losses of skin and required grafting that otherwise might have been avoided.

The typical Air Force or tank crew burn of the hands and face deserves special note. Hands should be ready for grafting in three weeks whether there are deep areas or not that will require later repair. To get a closed wound, or one as closed as possible, early grafting will save more hand function than any other procedure. Certainly immediate excision should not be carried out on the hands and face routinely, as to do so would destroy function and features unnecessarily. The Germans were known to have cut off both hands because of burns, apparently in the generally mistaken conception that the work would be lessened by anything that seemed easiest in the early care. This is appalling and could not take place where a philosophy as outlined here existed or where there was any feeling for the golden rule.

Whenever possible, good cleansing care and the application of fine 44 mesh greased gauze next to the wound are essential. That the fingers should be separated is obvious. If this cannot be done, then the whole area can be covered with the cleanest available material and evacuation completed promptly.

The face heals readily, but with extensive deformity if the burn is deep, as can be attested by hundreds of Air Force and tank crew members, so that the most exhausting secondary

repairs have to be made on all severely burned faces, many times involving grafting of the entire face and making eyelids, nose and ears.

Homografting can be done as emergency dressing of severe burns, and lives may thus be saved. These grafts do not persist, however, and later autograft repair will have to be done if the area is large or deformity persists.

Skin banks for homografting would be advantageous, but the practicability of them is difficult to establish, and in large hospital centers there is usually a source of fresh skin for use when needed. This is a field for research and advancement, but with homografts not persisting except in identical twins the ultimate advantage may not be too great.

There are important points about training surgeons to do skin grafting. Plastic surgeons are not needed to do flat surface grafting. They have developed a technic by which general surgeons can do it, and much of this type of work was done by young general surgeons so trained in World War II. At present we have one regular army officer in training, and we hope to have more to provide a source of supply of officers for taking care of severe burns that require grafting.

LIEUT. COL. EDWIN J. PULASKI (MC), Fort Sam Houston, Texas: During the past year our unit has been interested in the problem of infection in thermal burns. In 38 patients with

Bacterial Flora in Full Thickness Burns (23 Patients)

Organism	Total	Ps	As	Cs
Coagulase-positive hemolytic Staph. aureus	20	10	19	18
Hemolytic streptococci	2	2	2	2
Pseudomonas	10	0	3	6
Proteus	3	0	0	2
Aerobacter	3	0	1	2

fresh partial or full thickness burns admitted directly to the hospital, wound suppuration with or without fever developed in 11. Infection was already present in an additional 12 patients who arrived in the hospital seven days or longer after injury. All patients received parenterally administered penicillin. Hemolytic streptococci were isolated in only two instances and did not persist or appear to be responsible for invasive infection. It is inferred that contamination by the hemolytic streptococcus does not offer a serious problem in the burned patient receiving penicillin. Coagulase-positive hemolytic Staph. aureus was isolated in nearly all instances of wound suppuration. In one half of the cases it was accompanied with Pseudomonas, Proteus or Aerobacter organisms. Fifty per cent of the staphylococci were penicillin resistant. This increased incidence of resistance becomes more significant when the equally high occurrence of penicillinase-producing gram-negative bacteria is considered. Penicillin-sensitive staphylococci became resistant to the drug during therapy in only one of 10 cases. Less than 10 per cent of the staphylococci were resistant to aureomycin and chloramphenicol. The only conclusion is that penicillin as well as the newer broader spectrum antibiotics have eliminated the threat of invasive infection in the burned patient. In our experience no antibiotics, parenterally or locally administered, effectively suppress wound suppuration so long as necrotic material is present.

Maintenance of nutritional balance, excision of devitalized tissue, immobilization, simple cleansing measures applied to the open burn and surrounding intact skin and free drainage aided by the use of dressings with a high absorptive capacity continue to be the most effective means of minimizing sepsis until conditions obtain for surgical revision and skin cover.

CORROSIVE INJURY OF THE STOMACH

Report of a Case Caused by Ingestion of Clorox® and Experimental Study of Injurious Effects

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CICATRICIAL injuries of the esophagus caused by the ingestion of corrosive substances are common and combined injuries of the stomach and esophagus somewhat less common. Injury of the stomach alone is encountered much less frequently. In a recent review Strode and Dean [1] collected 12 cases of pyloric stenosis resulting from the swallowing of corrosive substances in the American literature and a total of 140 cases from the world literature. The cases reported by Vinson and Harrington [2] and by Schulenburg [3] are examples of cicatricial injury of the stomach without esophageal damage, the former resulting from ingestion of formaldehyde and the latter from ingestion of hydrochloric acid.

Numerous agents have been responsible for injuries of the esophagus and stomach, usually strong acids or alkalis. Acid injuries of the stomach are far commoner than alkali injuries, whereas the reverse is true of the esophagus. We have been unable to find in the literature any case of severe injury to either the esophagus or the stomach following the ingestion of clorox,® a commercial preparation which consists of 5.25 per cent sodium hypochlorite by weight in water, with a p_H of 10.8. The only instance of injury from clorox® which we have found recorded was a mild esophageal injury of a diffuse erythematous nature not resulting in a stricture which was included in Uhde's [4] report of 34 chemical burns of the esophagus. We have recently treated a severe cicatricial injury of the stomach without esophageal involvement which followed the ingestion of clorox® and have been prompted by this experience to conduct some experiments relating to tissue damage from this material.

From the departments of surgery and biochemistry, Indiana University School of Medicine.

1. Strode, E. C., and Dean, M. L.: Acid Burns of the Stomach, Ann. Surg. **131**:6801-6811, 1950.

2. Vinson, P. P., and Harrington, S. W.: Cicatricial Stricture of the Stomach Without Involvement of the Esophagus Following the Ingestion of Formaldehyde, J. A. M. A. **93**:917-918 (Sept. 21) 1929.

3. Schulenburg, C. A. B.: Corrosive Stricture of the Stomach Without Involvement of the Esophagus, Lancet **2**:367-368, 1941.

4. Uhde, G. I.: Chemical Burns of the Esophagus, Ann. Otol., Rhin. & Laryng. **55**:795-820, 1946.

REPORT OF A CASE

The patient was a white male painter 49 years of age who entered the hospital on Aug. 12, 1949, complaining of inability to retain food. On April 22 he had attempted to commit suicide by cutting his wrists and throat and by drinking approximately 1 quart (1,000 cc.) of clorox.® He had been nervous for about three years and had had numerous episodes of severe depression. After the attempt at suicide, he was hospitalized elsewhere for five weeks. A tracheotomy tube was initially required because of a laceration of the trachea. Numerous blood transfusions were given. After his discharge he was able to eat well until three weeks before his admission on August 12, at which time he began to have difficulty swallowing both solid and liquid foods. His weight decreased 10 to 20 pounds (4.5 to 9 Kg.). He regurgitated practically all foods immediately after ingesting them.

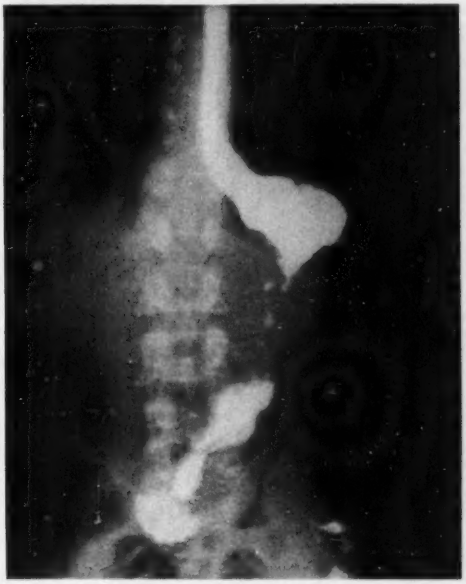

Fig. 1.—Preoperative roentgenogram with barium swallow showing stenosis of stomach.

Physical examination revealed a cooperative, emaciated man with an anxious expression. There was evidence of considerable loss of weight. He was fairly well hydrated. The rest of the examination revealed nothing remarkable except for scars on the flexor surfaces of the wrists, which limited extension of the left hand, and a transverse scar in the neck just above the sternal notch.

Urinalysis and a serologic test gave negative results. The hemoglobin content was 14.5 Gm. per 100 cc., and there were 8,050 leukocytes, with a normal differential count. The total serum protein count was 7.2 Gm. per 100 cc., with albumin 4.35 Gm. and globulin 2.85 Gm. The non-protein nitrogen was 29 mg. per 100 cc. On gastric analysis 25 cc. was aspirated, with a total acidity of 179 and no free hydrochloric acid.

Roentgen examination of the gastrointestinal tract on August 16 revealed no abnormality of the esophagus. The barium sulfate entered the stomach and stopped in the cardiac portion, only a narrow stream of the material entering the pyloric area (fig. 1). The impression was that marked constriction of the stomach due to scarring and fibrosis was present. The presence of a

neoplasm, however, could not be definitely ruled out by this examination. The roentgenogram of the chest was considered normal. Esophagoscopy demonstrated a normal esophagus throughout its entire length; the cardia was also visualized and appeared normal. The psychiatric consultant felt that there was no contraindication to operation.

On August 26, the abdominal cavity was explored through a left upper rectus incision. There was found a small contracted stomach, measuring approximately 9 cm. over its entire length from cardia to pylorus. Much fibrosis and puckering of the entire stomach could be seen. There was no evidence of a malignant process. The rest of the abdomen was normal. The incision was extended up through the ninth interspace and the thorax entered. The diaphragm was split in

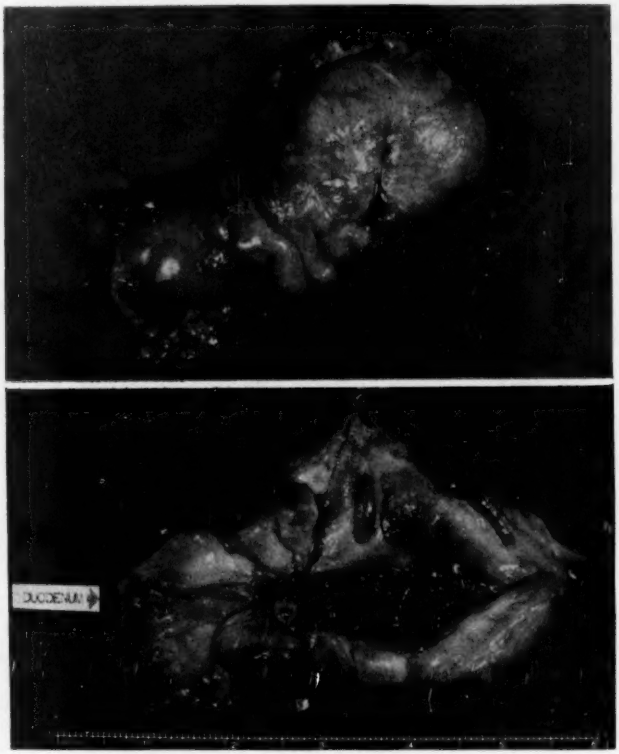

Fig. 2.—Photograph of specimen removed at operation. The small size of the stomach and the thickness of its wall is evident.

the direction of its fibers up to the esophageal hiatus. The triangular ligament of the liver was severed. A total gastrectomy was performed, and an end to side esophagojejunostomy was constructed with an enteroenterostomy between the two loops of jejunum. The patient stood the procedure well.

Gross examination of the organ revealed extensive scarring in the stomach wall, with a shallow ulceration on the lesser curvature (fig. 2). The thickness of the wall varied from a few to 15 mm. In the midportion the scarring was so extensive that the lumen was almost obliterated. The luminal diameter at this point was approximately 3 mm. The inner part of the wall was firm, while the serosa was soft and thrown into thick folds. Histologic examination revealed

that the thickening was due to fibrosis in the mucosa and submucosa. The superficial epithelium was largely desquamated, and the normal glandular pattern was markedly altered (fig. 3).

Postoperatively, for 48 hours the patient received intravenous injections of blood, plasma, dextrose and amino acids. He was then given gradually increasing amounts of fluids orally. On the sixth postoperative day he was able to take a soft diet of six small feedings. His early tendency to regurgitate bile was adequately controlled with mild sedation and antispasmodics.

A postoperative barium swallow showed adequate passage of the material into the jejunum and no dilatation of the esophagus. Laboratory examination before discharge revealed a hemoglobin content of 12.5 Gm., 4,510,000 erythrocytes and 6,350 lymphocytes. The total protein value was 5.1 mg. per 100 cc. in spite of a high protein intake. During the latter part of the patient's hospital stay he again became depressed. He was discharged on September 18 to be followed in the surgical and psychiatric outpatient clinics.

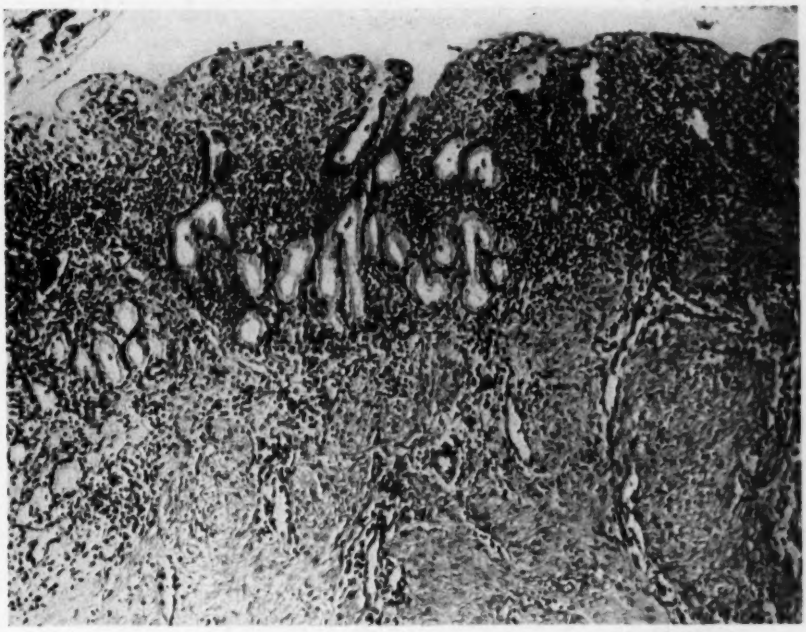

Fig. 3.—Photomicrograph of section of stomach removed from the patient.

The patient failed to return to the outpatient clinic for three months, and during this time he became more depressed, with paranoid trends and suicidal intentions. He was sent to a closed psychiatric ward, in another institution, from which he was committed to a state psychiatric hospital a few months later. While on the psychiatric ward he often refused food, although it was reported that he could eat without difficulty.

During a recent interview, nine months after operation, he appeared in good physical condition and was able to take the institutional diet as well as the other inmates. He had no vomiting and no abdominal complaints.

EXPERIMENTAL DATA

The effect of clorox® on the stomach of dogs was studied. One hundred cubic centimeters of undiluted clorox® was administered by tube. Immediately after removal of the tube the animal salivated profusely and vomited watery material

mixed with bright blood. Diarrhea soon occurred. The dog died the next day, and autopsy revealed extensive hemorrhage in the wall of the stomach and esophagus.

In an attempt to prevent vomiting of the administered clorox,* a tube with an inflated balloon was used in three other anesthetized dogs. Twenty-five cubic centimeters of undiluted clorox* was given. The cuff was kept inflated and pulled snugly up against the cardia for 25 minutes before the tube was removed. No vomiting was noted. One dog died in one month; the other two were killed in three months. At autopsy the first animal was emaciated and the esophagus was greatly

TABLE 1.—*Extent of Injury to Abdominal Skin of Rabbits Following Exposure to Clorox* Diluted with Various Body Fluids*

Body Fluid Added to Clorox*	Clorox*: Body Fluid Ratio	pH	Relative Degree of Injury†			
			15 Min. Exposure		30 Min. Exposure	
			Applied Immediately After Mixture	Applied 5 Min. After Mixture	Applied Immediately After Mixture	Applied 5 Min. After Mixture
Gastric juice‡	2:1	7.5	2+	2+	2+	1+
Plasma	2:1	7.5	0	0	0	0
Saliva	2:1	7.6	4+	3+	4+	4+
Water	2:1	10.0	3+	4+	3+	4+
Gastric juice and plasma	2:1:1	8.5	1+	1+	1+	0
Saliva and plasma	2:1:1	8.73	1+	1+	1+	1+

* Registered trademark.

† In this and the following tables the injury was graded on a basis of 0 to 4+, the last grade being the severest.

‡ Unmixed gastric juice was found to be noninjurious.

TABLE 2.—*Relationship of pH to Injury to the Abdominal Skin of Rabbits Following Exposure to Clorox* Mixed with Body Fluids*

Body Fluid Added to Clorox*	Clorox*: Body Fluid Ratio	pH Before Adjustment	pH After Adjustment	Relative Injury
Gastric juice	2:1	8.5	7.5	1+ to 2+
Saliva	2:1	9.5	7.5	4+
Water	2:1	10.15	7.5	3+
Plasma	2:1	9.5	7.5	0
Plasma and HCL	2:1:1	4.0	4.43	0
NaOH	No clorox* added	11.45	11.65	0

* Registered trademark.

dilated. The stomach and the small intestine appeared grossly normal. The esophageal mucosa appeared denuded, but no gross hemorrhagic areas were seen. When the other animals were killed, the esophagus, stomach and duodenum were grossly normal except in one animal, in which the pylorus was thickened and would not admit a finger. The stomach itself in both animals showed no evidence of stricture or fibrosis. The esophageal mucosa was slightly blanched.

Histologic studies of tissue removed at autopsy from the animal which died in 24 hours revealed notable congestive changes in the esophagus, stomach and duodenum. The mucosa of these organs was edematous, with destruction of the glandular pattern, and greatly infiltrated with polymorphonuclear leukocytes. The blood vessels were distended, and much evidence of hemorrhage could be seen. These changes extended throughout the mucosal and submucosal layers.

Organs removed from the three other dogs showed some alteration of the glandular pattern of the esophagus, stomach and duodenum, with some fibrosis, particularly in the submucosa, and a scattered infiltration of the mucosa, submucosa and superficial muscular layers with lymphocytes. There were no congestive changes.

In an effort to determine the reaction responsible for injury to tissue, a number of other experiments were carried out. Clorox® was mixed in ratios of 2:1, 1:1 and 1:2 with water, saliva, gastric juice and plasma. These mixtures were applied to the shaved abdominal skin of anesthetized rabbits in inverted tubes for 15 and 30 minutes. In one experiment all the solutions were buffered to the same p_H before being applied to the skin. As can be seen from tables 1 and 2 and figure 4, the same

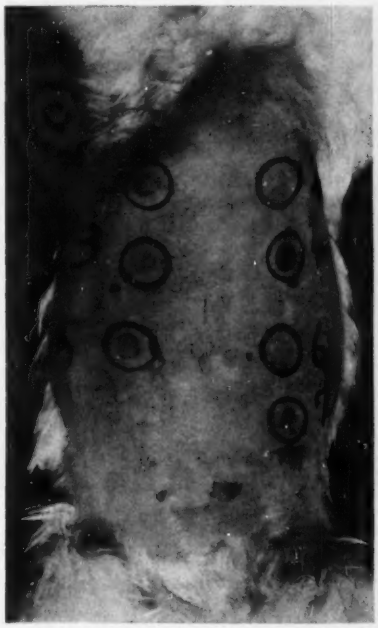

Fig. 4.—Photograph of abdomen of a rabbit showing the extent of injury to the skin 24 hours after application of various solutions containing clorox.® The skin inside the various circles was in contact for 15 minutes with the following solutions: (1) clorox® and gastric juice, 2:1; (2) gastric juice; (3) clorox® and plasma, 2:1; (4) clorox® and saliva, 2:1; (5) clorox® and water, 2:1; (6) clorox,® gastric juice and plasma, 2:1:1; (7) clorox,® saliva and plasma, 2:1:1.

solutions were responsible for the greatest tissue damage in each study, regardless of the dilution or the p_H. The decomposition of clorox,® as evidenced by the liberation of gas, was greatest when it was mixed with plasma, and yet the plasma-clorox® preparations caused definitely less damage to the rabbits' skin than the other solutions. It was felt that the proteins in the solutions containing plasma probably reacted in such a way as to buffer the harmful action of clorox® on tissue.

This protective action of proteins appears to have been demonstrated in still other experiments. The feet of anesthetized white rats were immersed in similar

solutions and in mixtures of clorox* with various protein substances. Tables 3 and 4 and figure 5 show the comparative damage to the rats' feet from those various solu-

TABLE 3.—*Injury to the Feet of a Rat Following Immersion in Clorox* Mixed with Body Fluids in a Ratio of 2: 1*

Body Fluid Added	Injury After Immersion for 15 Min.
Gastric juice	1+ (edema)
Saliva	3+ (bleeding and edema)
Water	4+ (bleeding and edema)
Plasma	0

* Registered trademark.

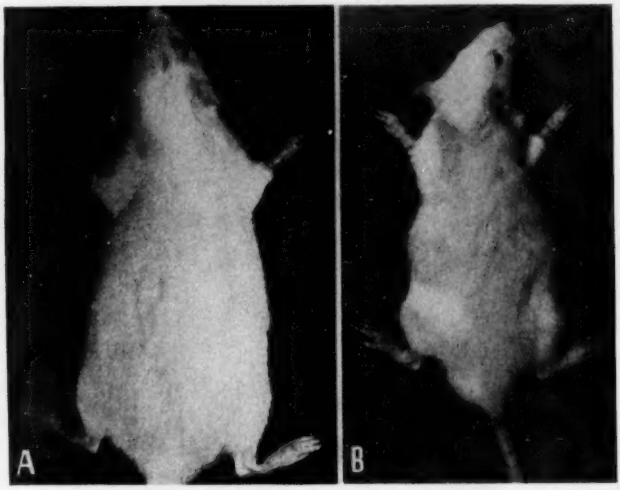

Fig. 5.—*A*, photograph showing the degree of injury to the feet of a white rat when immersed in the following solutions containing clorox*: (1) right front foot, clorox* and saliva; (2) left front foot, clorox* and water; (3) right hindfoot, clorox* and plasma; (4) left hindfoot, clorox* and gastric juice. *B*, photograph showing injury to the feet of a white rat when immersed in various clorox solutions containing added proteins: (1) right front foot, clorox,* water and milk; (2) left front foot, clorox,* water and egg white; (3) right hindfoot, clorox,* water and horse meat; (4) lef hindfoot, clorox* and water.

TABLE 4.—*Injury to the Foot of a Rat Following Immersion in Clorox* Diluted 2: 1 with Water and Mixed with Suspensions of Various Protein Substances in Ratio of 2: 1*

Substance Added	Injury After Immersion for 15 Min.
Egg white	0
Milk	0
Horse meat	1+ mild edema
Clorox + water, nothing added	4+ edema

* Registered trademark.

tions. It is evident that added proteins in the form of plasma, egg white, milk and, to a slightly lesser extent, macerated horse meat, did in some manner protect the tissue from the action of the clorox.* When the feet were immersed in solutions of clorox* and water and clorox* and saliva, the reaction was marked, with extreme

edema, bleeding and actual ulceration and destruction of tissue. There was no visible damage to the feet when plasma, milk and egg white were added and only a slight reaction when macerated horse meat was used.

It would appear that in these experiments the presence of large amounts of proteins did afford some protection. This protective effect seems related to the amount of free protein in the solution available for reaction with the clorox.® Though plasma added to clorox® in the ratio of 1:2 resulted in no injury, plasma added to clorox® in the ratio of 1:10 and kept in contact with the foot of a white rat for the same period caused as severe damage as resulted from water or saliva and clorox.®

COMMENT

The reaction of hypochlorite with proteins has been described by Baker [5] and other investigators. Chlorination and oxidation occur when sodium hypochlorite is in contact with amino groups. Protein, if in sufficient quantity, thus absorbs considerable amounts of the liberated active chlorine and oxygen which would otherwise attack living tissue. This observation suggests that readily available protein substances, milk and egg white, may be used as a first aid measure after the ingestion of hypochlorite and similar solutions.

Previous investigators have shown that pyloric and antral spasm plays an important role in the production of the injury which follows the ingestion of corrosive substances. Testa is cited by Schulenburg [3] as having observed severe preantral spasm when he put caustic soda plus barium into the stomachs of dogs with a tube. He noted that the trauma was worse in the area along the lesser curvature, just superior to the area of spasm. Stricture of the stomach developed in his animals one month after injury. It has been the experience of most investigators that injury after the ingestion of corrosive agents is greatest along the lesser curvature in the prepyloric region.

The case which we have reported appears remarkable in several ways. In the first place, it occurred after the ingestion of what has been sold commercially as a rather harmless solution and is so labeled. Secondly, the stomach was severely damaged without apparent injury to the esophagus, an uncommon occurrence. Finally, the injury was of an extreme degree. The stomach was greatly thickened, fibrotic and almost entirely stenosed, with only an extremely small lumen remaining. The damage extended throughout the entire length of the organ, which had contracted to a length of only 9 cm. This severe cicatricial injury can probably be attributed to the large amount of clorox® ingested, to the fact that the stomach was empty at the time and to the rapid dissociation of the hypochlorite by gastric juice without sufficient protein to provide protection. It may be significant that the tracheal laceration, functioning as an open tracheotomy, may have prevented the patient from vomiting much of the material.

SUMMARY

A case of severe cicatricial injury to the stomach following ingestion of clorox® and necessitating total gastrectomy is reported. Experiments are reported demonstrating that clorox® mixed with water, gastric juice or saliva is extremely injurious to living tissue. Various protein substances appear to afford some protection against such injury.

5. Baker, R. W. R.: Studies on the Reaction Between Sodium Hypochlorite and Proteins: I. Physico-Chemical Study of the Cause of the Reaction, Biochem. J. 41:337-342, 1947.

TRAUMATIC ANEURYSM AS A COMPLICATION OF SUPRACONDYLAR FRACTURE OF THE HUMERUS

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IN CIVILIAN life the occurrence of traumatic aneurysm is rather infrequent, but in time of war the incidence of aneurysm and arteriovenous fistula in battle casualties is high. Bigger [1] reported a personal series of civilian cases in which traumatic aneurysm or arteriovenous fistula developed secondary to bullet or stab wounds and has described the problems and treatment in these conditions. Shumacker and Carter,[2] Albright and Van Hale,[3] Preston,[4] Beck,[5] and many others have reported various types of vascular injuries.

Traumatic aneurysm of the brachial artery is a rare complication of a supracondylar fracture of the humerus, yet numerous cases of traumatic aneurysm of the brachial artery, the result of bullet or knife wounds, have been reported. The case here presented is interesting not only because of the infrequency of its occurrence but because of the problems presented in diagnosis and treatment.

REPORT OF A CASE

On Sept. 22, 1949, an 11 year old boy was admitted to the Cook County Children's Hospital because of a painful swelling of the left elbow. His grandmother stated that on August 5 he had fallen from a tree, sustaining a fracture of his arm. About six hours after the accident he was taken to a hospital in a neighboring city, where a roentgenogram showed a supracondylar fracture of the humerus. The fracture was manipulated with the patient under general anesthesia and later was immobilized in a cast (fig. 1).

On the patient's admission to Cook County Hospital, examination revealed a thin youth who was nervous and obviously uneasy about his injured left arm. The temperature was 99.2 F. His general physical condition was good. When the posterior splint was removed from the arm, the skin in the region of the elbow and over the forearm was dry and showed a brownish discoloration. The entire elbow was three to four times larger than normal because of a huge warm swelling of the antecubital fossa. Tenderness to palpation was observed. No pulsation was felt over this mass. The limitation of motion was such that the boy cried out with pain at any attempt to move the arm. The forearm, hand and fingers were so swollen that

From the Department of Surgery, University of Illinois College of Medicine and Cook County Hospital.

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5. Beck, W. C.: "Pulsating" Hematoma (False Aneurysm), War Med. **4**:502, 1943.

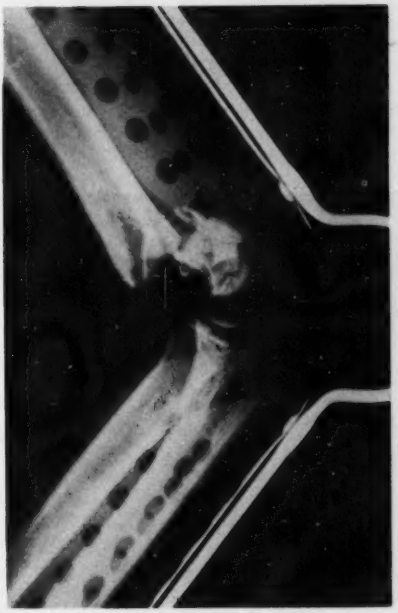

Fig. 1.—Original roentgenogram taken at outside hospital at time of injury, showing characteristic lateral view of a supracondylar fracture of the humerus. Observe the degree of soft tissue swelling as compared to that shown in the roentgenogram (fig. 3) taken on admission to Cook County Hospital. (The anteroposterior view was not acceptable because the metal splint obliterated the fracture.)

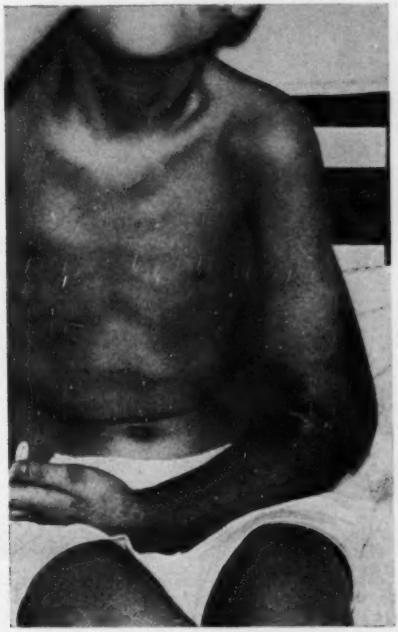

Fig. 2.—Appearance of the elbow and forearm. Note the swelling in the antecubital fossa, the edema of the forearm and hand and the brown pigmentation of the skin of the arm and forearm.

the hand was almost useless. The hand was warm and of good color. Pitting edema was present. The radial pulse was not palpable. No sensory changes were apparent (fig. 2). A hematoma or an abscess was considered in the diagnosis.

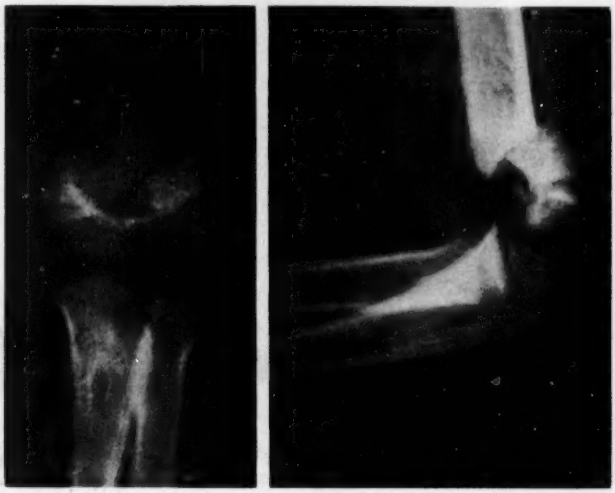

Fig. 3.—Roentgenograms taken on patient's admission to Cook County Hospital showing extent of healing of the supracondylar fracture, with good alinement in the anteroposterior view and fair alinement in the lateral view. In addition, there is evidence of a pronounced soft tissue swelling in the region of the antecubital fossa.

Fig. 4.—Photograph taken just before operation shows the decrease in swelling in the region of the elbow after the application of the pressure dressing and immobilization of the arm in traction. Compare this photograph with the one taken on admission (fig. 2).

Roentgenograms taken on the patient's admission showed a fairly good reduction of the supracondylar fracture. There was considerable evidence of new callus formation and of

periosteal reaction at the level of the fracture. Atrophy of the bones was apparent. There was also evidence of soft tissue swelling (fig. 3).

The boy was placed in bed, with the arm held in a sling. The swelling of the forearm and hand subsided somewhat, but the enlargement of the antecubital fossa remained unchanged.

On Oct. 1, 1949, with the patient under general anesthesia, aspiration of the nonpulsating mass was done. A large amount of bright red blood was removed under pressure through

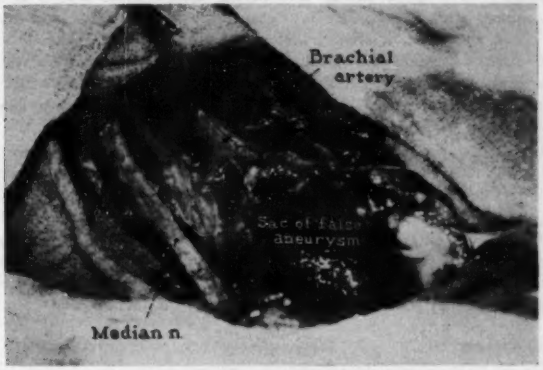

Fig. 5.—Photograph taken at operation showing the aneurysm which developed after injury to the brachial artery. Note the displacement of the median nerve to the inner side of the arm.

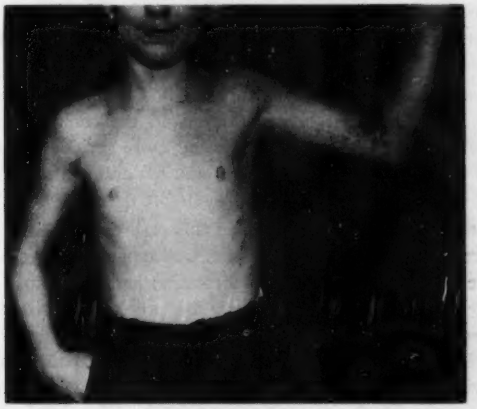

Fig. 6.—Photograph taken nine weeks after operation. Note the reduction in size of the arm. There is some residual pigmentation of the skin in the antecubital fossa. The swelling has disappeared. Note the position of the operative scar.

a 15 gage needle. A traumatic or false aneurysm was suspected. A pressure dressing was applied. On his return to bed the patient's arm was placed in a suspension traction set-up, with the upper arm abducted and the forearm flexed. In this position the swelling partially subsided. Some time later, for the first time, a systolic bruit was heard along the anteromedial aspect of the mass, but no thrill was present. The peripheral circulation to the hand appeared adequate as the hand and fingers continued to have good color and temperature (fig. 4). Arteriograms were considered but were not done.

On Nov. 8, 1949, the patient was returned to the operating room. A tourniquet was applied to the upper part of the arm. Exploration of the antecubital fossa demonstrated a large false aneurysm of the brachial artery which displaced the median nerve to the inner side of the arm (fig. 5).

The brachial artery was dissected out above and below the mass. After evacuation of the clots of old blood and irrigation of the aneurysmal space with saline solution, the tourniquet was released temporarily. The defect in the wall of the artery, about 2 mm. in diameter, was identified and sutured with fine 00000 silk. Because the sac was large and densely adherent to other soft tissue structures, it seemed best not to dissect it out. The median nerve was restored to its normal position. Excellent peripheral pulsations continued. The wound was closed with surgical gut, with a small Penrose tube left in place for drainage. A moderately firm pressure dressing was applied, followed by a posterior molded plaster splint. A blood transfusion was given during the operation.

On November 20 the patient was discharged. The arm showed considerable improvement. The elbow was much reduced in size, but some edema was still present. The motion of the elbow had increased a few degrees. The boy was instructed to use his arm, and physical therapy was started.

On Jan. 14, 1950, the patient was reexamined. There was restriction of movement in the elbow joint, with only 10 to 15 degrees of motion. There were good pronation and supination of the forearm (fig. 6). The operative scar was well healed. The radial pulse was strong. Sensation was not impaired. The boy was urged to continue physical therapy and encouraged to use the arm.

COMMENT

This presentation concerns an 11 year old boy admitted to the Cook County Hospital children's surgical service six weeks after treatment of a supracondylar fracture of the left humerus. A traumatic aneurysm of the brachial artery was found and successfully treated. It is difficult to say in this case whether the injury to the artery was part of the original fracture or whether the hematoma developed secondary to manipulation and reduction.

We have used the suspension traction method, emphasized by Dunlop,[6] for this type of injury in children in order to avoid the complications of a severe supracondylar fracture of the humerus. In the more serious cases,[7] skeletal traction has proved more efficient and produces and maintains a satisfactory reduction without further injury to the already damaged soft tissues.

During the first weeks of observation in this case the swelling about the elbow was tense and warm, but no distinct pulsation was apparent over the mass. Aspiration of the tense mass ruled out abscess formation as bright blood under pressure was obtained. It was then apparent that the problem consisted of an arterial hematoma subsequent to a supracondylar fracture of the humerus, possibly a false aneurysm. After the aspiration, pressure was applied to the mass in the antecubital fossa, with the arm suspended in traction for two weeks. During this time the edema of the hand and forearm subsided. The delay in surgical intervention afforded greater opportunity for the development of a collateral circulation.

Albright and Van Hale [8] state that partial division of an artery or of an artery and vein, if treated expectantly, and it usually is, will lead to a pulsating hematoma

6. Dunlop, J.: Transcondylar Fracture of the Humerus in Childhood, J. Bone & Joint Surg. **21**:59, 1939.

7. Miller, E. M.; Fell, E. H., and Brock, C. E.: Progress in Treatment of Severe Supracondylar Fractures of the Elbow, Proc. Inst. Med. Chicago **13**:128, 1940.

and thence to a traumatic aneurysm. In this case no significant pulsation was palpable over the mass until after the aspiration of blood some weeks after the initial injury.

In this case the treatment at first was conservative in order that sufficient time might elapse for the development of collateral circulation as well as for the subsidence of the edema and of the interstitial hemorrhage in the damaged vessel. According to Julian,[8] the ideal operative aim should be the repair of the vessels. When this is impossible, the treatment may be ligation above and below the defect with transection, the ligatures being placed close to the defect so as to avoid the collateral branches. Fortunately, primary closure of the laceration in the vessel was accomplished successfully without interruption of the circulation.

It is interesting to note that although at operation the median nerve was found to be displaced to the inner side of the forearm by the aneurysm there was no evidence of nerve impairment. Elkin and Woodhall[9] report two arterial aneurysms of the brachial artery in the antecubital space, the result of gunshot wounds, which were associated with nerve injury. They advocate resection of the arterial aneurysm rather than endoaneurysmorrhaphy when concomitant nerve injury is present. In 1946 Shumacker and Carter[2] reported that in a large number of patients with traumatic aneurysm or arteriovenous fistula the commonest complication was an associated peripheral nerve injury. They further stated that in their series 73 of 119 patients with arterial aneurysm had associated nerve palsy. In approximately two thirds of these 73 patients neurolysis or neurorrhaphy was necessary. In the majority of these cases the initial trauma was considered to be the cause of the associated nerve dysfunction, whereas in others damage to the nerve was by pressure of the aneurysm. According to these authors, early operation is not imperative unless there is associated severe nerve paralysis or an external rupture of an aneurysm or fistula. It is generally agreed, however, that once localization has occurred surgical intervention should be delayed to permit improvement in the collateral circulation and disappearance of bacteria from the adjacent tissues. Unless complications arise which demand earlier operation, conservative treatment should be continued for at least six to eight weeks.

The physiological effects of arterial aneurysms, according to Bigger,[1] are less complex than those of arteriovenous fistulas. With an arterial aneurysm the effects are largely confined to the area supplied by the injured artery, whereas an arteriovenous fistula may produce pathological effects on the entire circulatory system. This should be kept in mind in the management of the two conditions, but the same general principles are applicable in their treatment.

In this patient a hematoma or a false aneurysm was suspected, but it was not until aspiration of the mass revealed blood that the diagnosis was confirmed. Some time after this a systolic murmur was heard for the first time over the midportion of the mass. It has been observed by others that the systolic bruit typical of pulsating hematoma and false aneurysm may not be present in the early days after injury.

8. Julian, O. C.: Symposium on Minor Surgery: Peripheral Arterial Obstruction, S. Clin. North America **28**:154, 1948.

9. Elkin, D. C., and Woodhall, B.: Symposium on Vascular Surgery: Combined Vascular and Nerve Injuries of Warfare, Ann. Surg. **119**:411, 1944.

Conway and Plain [10] emphasize that true pulsating hematomas in which the clot has not liquefied give rise to a bruit that is only faintly audible but as the false aneurysmal sac forms and the clot liquefies the bruit becomes more intense.

SUMMARY

A case is presented of a traumatic aneurysm of the brachial artery occurring as a complication of a supracondylar fracture of the humerus. The diagnosis of the mass in the antecubital fossa was questionable until aspiration proved the presence of blood. Operation was deferred for a number of weeks after the diagnosis was made in order to permit the development of an adequate collateral circulation.

It has been suggested that the ideal treatment of an injured vessel with an associated hematoma or traumatic aneurysm is repair of the defect rather than ligation and transection of the damaged vessel. In this case it was possible to suture the laceration of the vessel successfully. The aneurysmal space was drained, while the wall of the sac was left intact.

During manipulation and reduction of any fracture, undue trauma to the blood vessels and soft tissues should be avoided. The method of skin traction emphasized by Dunlop or the technic of skeletal traction suggested by Miller and Fell is recommended in the treatment of severe supracondylar fractures of the humerus.

122 South Michigan Avenue.

5 South Wabash Avenue.

10. Conway, H., and Plain, G.: "Pulsating" Hematoma, False Aneurysm, and Arteriovenous Fistula Due to War Injuries, Surgery **19**:383, 1946.

CLINICAL FACTORS AFFECTING MORTALITY IN STRANGULATED HERNIA

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AND
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CHICAGO

STRANGULATED hernia is one of the few surgical emergencies for which published statistics do not show an appreciable decline in mortality in recent years. This fact has led to a renascence in experimental investigation of the condition in an attempt to search for factors other than those known to respond to present day therapy. The mortality rate reportedly ranges from 20 to 40 per cent in cases presenting interference with circulation of the involved segment of bowel and is over 50 per cent in cases requiring resection.[1]

These widely quoted high mortality rates for strangulation obstruction and especially for resection, though not necessarily accurate today, still exert an unfortunate influence in that they might perhaps be used to distort the surgical approach to the problem in several ways: (1) the tendency to expect a high mortality rate might falsely justify a death; (2) resection, conceivably a life-saving measure, might be postponed or allayed in a futile and time-consuming effort to revive dead bowel; (3) the tendency to replace bowel of questionable viability might exist in the hope that the reportedly lower mortality rates for this maneuver will mysteriously protect the patient.

In our opinion a reevaluation of the problem from the clinical standpoint is necessary in the light of recent investigative work and improved methods of management. This report concerns itself with an analysis of certain clinically measurable factors which might affect prognosis and mortality. We have analyzed a series of 100 consecutive cases of strangulated hernia in which operation was done at Michael Reese Hospital in the 15 year span from 1935 to 1949. In order to keep the problem clearly confined to cases in which there was definite interference with

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Read before the Chicago Surgical Society, April 7, 1950.

Mrs. Mildred Freud, statistician, prepared the statistical data in this report.

From the departments of surgery, Michael Reese Hospital and Northwestern University Medical School.

1. (*a*) McKittrick, L. S., and Sarris, S. P.: Acute Mechanical Obstruction of the Small Bowel: Its Diagnosis and Treatment, New England J. Med. **222**:611-622, 1940. (*b*) Schlicke, C. P.; Bargen, J. A., and Dixon, C. F.: The Management of Intestinal Obstruction: An Evaluation of Conservative Therapy, J. A. M. A. **115**:1411-1416 (Oct. 26) 1940. (*c*) Dennis, C., and Brown, S. P.: Treatment of Small Bowel Obstruction: Procedure Used at the University of Minnesota Hospital, Surgery **13**:94-106, 1943. (*d*) Calihan, R. J.; Kennedy, J. D., and Blain, A.: III. Intestinal Obstruction: Study of 204 Acute Cases with Reference to Possible Efficacy of Anti-Bacterial Therapy, Bull. Johns Hopkins Hosp. **79**:21-33, 1946. (*e*) Viability of Strangulated Bowel, Interim Report, Surgical Subcommittee of the Clinical Research Committee, Public Health Department, London County Council, Brit. M. J. **116**:43-46, 1948.

circulation, we included only those in which the bowel exhibited a definite change in color. Incarcerations without strangulation were not included.

We are enheartened by the fact that the results of the present study indicate that the mortality rate for strangulated hernia need no longer be high. Nor do we feel that it is necessary to implicate as causes for death factors other than those which we know as clinically tangible and which have been brought to light by the combined results of laboratory and clinical investigation.

The factors which we considered clinically measurable were age and sex, duration of symptoms, type of hernial constriction, length of the involved segment,

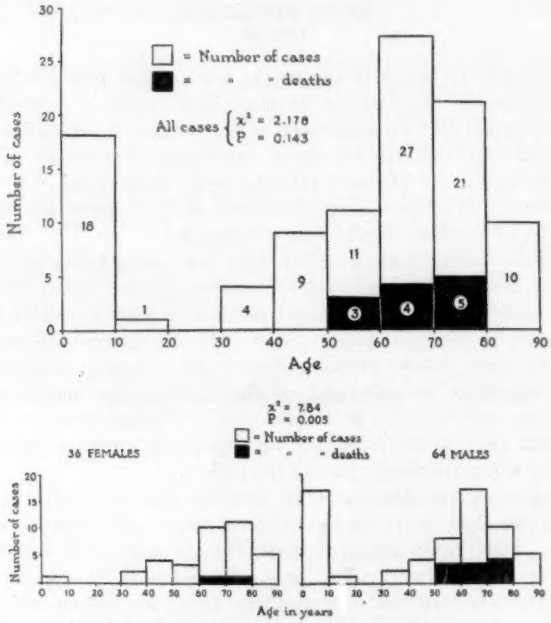

Fig. 1.—Age distribution and mortality.

character of the peritoneal fluid, type of operative therapy and preoperative and postoperative care. Our findings were subjected to statistical analysis in order to determine the significance of each factor as far as our sample would allow.

AGE AND SEX

The over-all mortality in this series was 12 per cent. Men constituted 64 per cent of the sample, while women represented 36 per cent. The mortality rate for men was 15.6 per cent and that for women 5.6 per cent. Subjection of these figures to statistical analysis revealed that the variation was not significant. The difference could have been due to chance 14.3 times out of 100 ($P = 0.143$). It is important to note that all the deaths occurred in the age group 50 through 79. This age group constituted 59 per cent of the total number of cases, while it accounted for 100 per cent of the deaths. The frequency histogram (chart 1)

indicates that if both sex and age are regarded in considering mortality the group with the highest rate is made up of men between the ages of 50 and 79. This group constitutes 35 per cent of the sample while it accounts for 83 per cent of the deaths.

As in so many other surgical conditions, another factor in a consideration of the infirmities of age is the presence of concomitant complicating diseases. In this series the average age of 46 patients with no other disease was 37.9 years. The average age of the 54 patients who entered the hospital with concomitant disease was 63.5 years. By far the commonest disease was arteriosclerotic coronary heart disease. There were three cases of heart disease with decompensation.

DURATION OF SYMPTOMS PRECEDING SURGICAL INTERVENTION

It is well known that the duration of symptoms prior to operation need not necessarily reflect the duration of strangulation. Incarceration with or without symptoms may occur and be present for a considerable length of time without strangulation. Laufman has demonstrated experimentally that the consequences of slow strangulation may be different from those of rapid strangulation.[2] The clinical reflection of these findings can be demonstrated by comparing the incidence of gangrene with the duration of symptoms in the present series. Patients with gangrene had symptoms prior to operation for periods ranging from five to 144 hours, while comparable periods for patients with viable bowel range from two to 120 hours. The practical importance of these figures lies in the fact that a patient may harbor gangrenous bowel after only five hours of symptoms, while it is possible that the bowel may be viable after 120 hours of symptomatic strangulation. The incidence of gangrene therefore bears no relation to the duration of symptoms.

On the other hand, the correlation between duration of symptoms and mortality rate appears to be direct (chart 2). In 64 per cent of the cases the duration of symptoms preceding operation was under 24 hours. There were two deaths in this group (17 per cent of deaths). In 29 per cent of the cases symptoms had been present for over 36 hours and there were nine deaths (75 per cent of deaths). The direct relationship between duration of symptoms and death becomes even more apparent when the group with symptoms under 60 hours is compared with the group with symptoms over 60 hours. The mortality for those with symptoms under 60 hours was 5 per cent, while the mortality for the group with symptoms over 60 hours was 58 per cent. These figures were found to withstand statistical analysis and are highly significant, indicating a definite relationship in this series between duration of symptoms and mortality.

TYPES OF HERNIA

Inguinal hernia accounted for 62 per cent of the strangulations, femoral hernia accounted for 19 per cent, and the remaining 19 per cent included ventral, umbilical and internal hernias. The high incidence of inguinal hernias with strangulation parallels, more or less, the natural incidence of this type of hernia. Since, as we have indicated, the deaths from strangulation occur chiefly in patients between the ages of 50 and 79, it would seem that elective repair of all hernias including the

2. (*a*) Laufman, H.: Gradual Occlusion of the Mesenteric Vessels: Experimental Study, Surgery **13**:406-410, 1943; (*b*) Gradual vs. Rapid Intestinal Strangulation, to be published.

inguinal type should be performed, certainly before the sixth decade (chart 3). Deaths from the various types of hernia show no significant predominance of one type over the other.

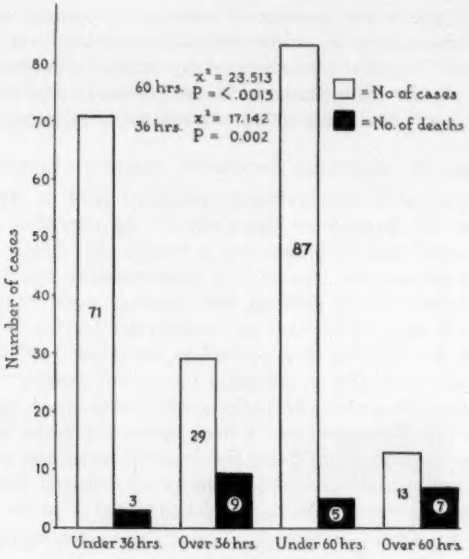

Fig. 2.—Duration of symptoms.

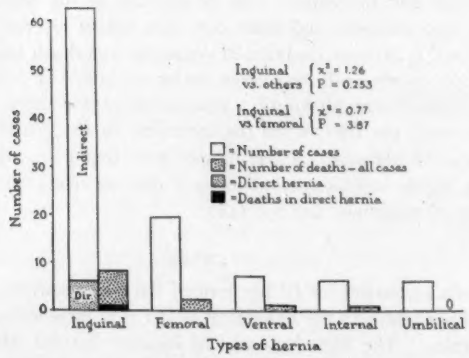

Fig. 3.—Types of hernia.

LENGTH OF INVOLVED SEGMENT

In 59 per cent of our cases the involved segment was less than 10 cm. in length. These 59 cases accounted for 25 per cent of deaths. Only 13 cases fell into the group in which the segment was over 30 cm. in length. However, these

13 cases accounted for 31 per cent of the deaths. If 30 cm. is arbitrarily chosen as the division between what could be called short and long segments, it is found that there were 79 cases with segments shorter than 30 cm., with 7 deaths, a mortality of 9 per cent. On the other hand, in 13 cases with segments over 30 cm. there were four deaths, a mortality of 31 per cent (chart 4). Statistical analysis of these figures indicates that they are significant and that the occurrence of a death in one or the other group could not have been due to chance in more than one in a thousand instances. Experimental conclusions which have indicated a high mortality in cases in which the involved segments were long are therefore

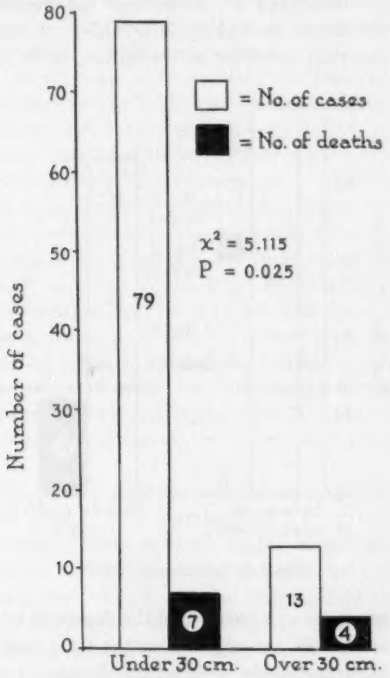

Fig. 4.—Length of segment.

directly reflected in a statistical analysis of human cases. In cases in which long loops are involved the additional fluid and blood loss undoubtedly plays an important role.[3]

CHARACTER OF PERITONEAL FLUID

In 93 instances the color and nature of the peritoneal fluid were recorded in operative notes. We found it convenient to divide the descriptions of fluid into

3. Scott, H. G., and Wangensteen, O. H.: Blood Losses in Experimental Intestinal Strangulations and Their Relationship to Degree of Shock and Death, Proc. Soc. Exper. Biol. & Med. **29**:424-427, 428-431, 559-561 and 748-751, 1932.

five groups: serous clear, serous turbid, serosanguineous clear, serosanguineous turbid and grossly bloody. It was remarkable that there were no deaths in instances in which the fluid was clear, regardless of whether it was serous or serosanguineous. All the deaths occurred in the group in which the fluid was turbid or bloody (chart 5). Statistical analysis is hardly necessary here except to point out that regardless of the cause of death, as will be discussed later, the presence of turbidity or of gross blood in the peritoneal fluid appears to be a bad prognostic sign.

In none of our cases, fortunately, was the fluid purple or black. Recent experimental work by Nemir and his associates [4] has indicated that the darker the fluid the higher the degree of toxicity in animals. It must be realized, however, that while an abnormal spectrum of the darker fluids characterizes toxicity

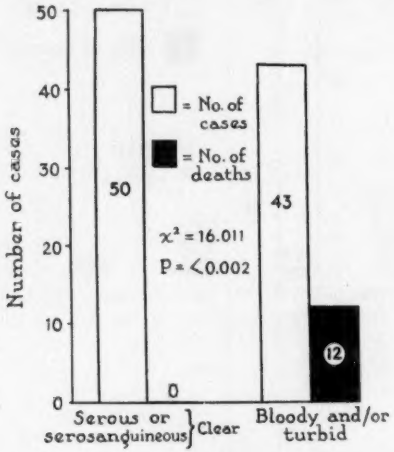

Fig. 5.—Character of fluid.

and has served experimentally as a measure of the degree to which it is present, no evidence is at hand to identify any pigment as the toxic factor. Experimentally the peritoneal fluid in strangulation obstruction changes from a pink, odorless, coagulable fluid to a reddish brown or black, malodorous, noncoagulable one. Bacterial enzymes such as streptokinase apparently render the fluid noncoagulable late in the disease.[5] Turbidity of the fluid is indicative of peritoneal reaction, with evidence of peritonitis, and must be considered as suggestive of permeation or perforation.

4. Nemir, P., Jr.; Hawthorne, H. R.; Cohn, I., and Drabkin, D. L.: The Cause of Death in Strangulation Obstruction: An Experimental Study; II. Lethal Action of the Peritoneal Fluid, Ann. Surg. **130**:874-880, 1949.

5. Tanturi, C. A., and Anderson, R. E.: Morbid Factors in Experimental Appendicitis, Surg., Gynec. & Obst. **89**:165-180, 1949.

OPERATIVE THERAPY

Local anesthesia was used in 48 cases, almost one half of the series. In 14 of these it was supplemented by some form of inhalation anesthesia. In 31 instances spinal anesthesia was employed, while in 21 cases inhalation anesthesia alone was used.

Tests for viability in this series consisted mainly of observing return of color, pulsations and peristalsis after treatment of the loop with warm packs and the administration of 100 per cent oxygen by inhalation. Recent experimental work [6] has emphasized that these criteria for viability are not infallible. The addition to the surgeon's armamentarium of vasodilating agents, such as papaverine for intravenous use, plus the employment of surface temperature readings,[7] might prove valuable in the future. In the few instances in which these adjuvants have been used they have been shown to be reliable.[8] It must be stressed that questionably viable bowel which cannot be definitely resuscitated should not be expected to survive simply because such measures have been employed.[9]

In 73 cases of bowel discolored by strangulation the surgeon judged the loop to be viable and replaced it in the peritoneal cavity. Errors in judgment were proved by postmortem examination in 3 cases, while in one other case the evidence was equivocal since no postmortem examination was allowed. One of the errors did not concern viability of the loop itself but consisted of overlooking a dangerously thinned-out band of bowel at the level of the released constriction ring. Perforation of this area resulted in peritonitis and death three days postoperatively. These cases constitute an incidence of error in judgment of about 4 per cent.

The mortality rate for replacement cases in this series was 7, or 9.1 per cent, roughly twice the percentage of error. It is obvious, therefore, that factors other than errors in judgment played a role in the mortality rate following replacement. A detailed account of these factors as we found them will be discussed in the analysis of deaths.

In 27 instances the bowel showed signs of irreversible infarction or frank gangrene. In four of these it was necessary only to invert a small gangrenous area by means of suture. There were no deaths in this group. In 19 cases a resection and anastomosis, with closure of the abdomen, were performed. Fourteen of the anastomoses were end to end, and five were side to side. In two of these cases a proximal decompressive ileostomy was performed. The number of deaths in the 19 cases of resection was three, or 15.8 per cent.

In two instances the surgeon elected to resect the segment and exteriorize the anastomosis. One of the patients died. In two other instances the loop was exteriorized without resection, and one of the patients died.

Thus the resection mortality in this series was 15.8 per cent, and the over-all deaths for 27 cases in which the loop had to be dealt with by one surgical means or

6. Laufman, H.: Experimental Evidence of Factors Concerned in the Eventual Recovery of Strangulated Intestine: Effects of Massive Penicillin Therapy, Surgery **28**:509-515, 1950.

7. Laufman, H., and Method, H.: The Role of Vascular Spasm in Recovery of Strangulated Intestine: Experimental Study, Surg., Gynec. & Obst. **85**:675-686, 1947.

8. Mason, M. L., and Ruge, D.: Spigelian Hernia: Report of a Case, Quart. Bull., Northwestern Univ. M. School **22**:71-73, 1948.

9. Grisell, T. L.: Complications in Treatment of Incarcerated Hernia with Vasodilatant Drug: Case Report, J. Indiana M. A. **42**:522-524, 1949.

another amounted to five, or 18.5 per cent. With such a small group it is not possible to draw statistically valid conclusions regarding the relative merits of resection over exteriorization. The recent literature, however, does indicate that resection offers better results today than do any of the exteriorization procedures. In a series of 33 cases of femoral hernia with gangrenous bowel reported from the Cook County Hospital by McNealy, Lichtenstein and Todd [10] in 1942, resection with end to end anastomosis in 13 cases resulted in a mortality of 61.5 per cent, while exteriorization in 11 cases gave a mortality of 81.8 per cent. Scudder and others [11] in 1938 reported 87 cases in which resection and primary anastomosis were performed, with a mortality of 59 per cent, while resection and enterostomy in 49 cases carried a mortality rate of 70 per cent and marsupialization in 42 cases, a rate of 83 per cent. Wangensteen [12] has recently stated that primary resection

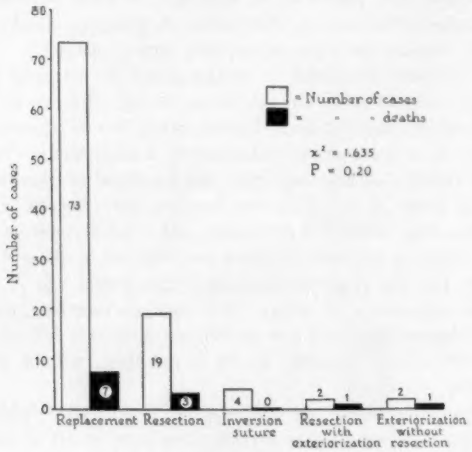

Fig. 6.—Type of operative treatment.

has come to replace exteriorization in the treatment of devitalized bowel in all types of strangulating obstruction in his clinic.

Moses [13] in 1946 reported a resection mortality of 85 per cent. Recently McLaughlin [14] reported 10 cases requiring resection, with a 50 per cent mortality.

10. McNealy, R. W.; Lichtenstein, M. E., and Todd, M. A.: The Diagnosis and Management of Incarcerated and Strangulated Femoral Hernia, Surg., Gynec. & Obst. **74**:1005-1010, 1942.

11. Scudder, J.; Zwemer, R. L., and Whipple, A. O.: Acute Intestinal Obstruction: Evaluation of Results in 2150 Cases; With Detailed Studies of 25 Showing Potassium as a Toxic Factor, Ann. Surg. **107**:161-197, 1938.

12. Wangensteen, O. H.: Intestinal Obstructions: A Physiological and Clinical Consideration with Emphasis on Therapy, Including Description of Operative Procedures, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1942, p. 363.

13. Moses, W. R.: Acute Obstruction of the Small Intestine: A Report of 118 Cases, New England J. Med. **234**:78-81, 1946.

14. McLaughlin, E. F.: Hernia in General Practice: Current Problems, J. A. M. A. **141**:1204-1208 (Dec. 24) 1949.

From Great Britain a report of results the country over for the years 1947 and 1948 showed a mortality rate of 56 per cent for 52 cases requiring resection.[1e] This series included patients operated on by practitioners in rural areas. In contrast to these high mortality rates, we noted Eliason's report in 1947 of 53 resections for strangulated bowel, with 10 deaths, or a 19 per cent mortality.[15] Dennis and Brown [1e] in 1943 reported on 18 patients with strangulation obstruction and gangrene, of whom 10 underwent resection and primary anastomosis. These 10 patients all recovered, as did two with exteriorization and delayed closure and one with inversion of a small gangrenous area. Five patients treated by exteriorization or other means died, giving a mortality rate of 27.8 per cent. This series was handled by one team of surgeons.

The University of Minnesota group [1e] emphasizes the importance of employing the closed aseptic technic in anastomoses following resection. The evidence from the present series does not substantiate this view, since all anastomoses were done by the open method, with no known ill effects.

PREOPERATIVE AND POSTOPERATIVE CARE

It need hardly be mentioned that good preoperative and postoperative care is as important as the operation itself. It is generally agreed that the crucial points in preoperative and postoperative care of patients with intestinal obstruction depend on the intelligent use of such therapeutic measures as (1) suction, (2) intravenous fluid and electrolyte therapy, (3) blood and plasma therapy and (4) antibiotic therapy.

Suction.—In the present series it was the almost universal practice to insert a Levin tube preoperatively when distention was present. If the patient was admitted with symptoms of more than 48 hours' duration, suction was maintained while he was being prepared for operation. If an obvious external strangulating hernia was present and distention was not great, a Levin tube was not inserted unless distention occurred in the postoperative period. The main use of suction was made in the postoperative period, although in 28 instances no suction was used at any time. In these cases the patients were given nothing by mouth until peristalsis returned postoperatively. In cases in which suction was used it was maintained until auscultatory signs of the return of peristalsis occurred or the distention disappeared.

Fluids and Electrolytes.—It is difficult to record generalities in regard to the intravenous use of fluids and electrolytes in a series such as this, since the type and amount of fluids were considered individually for each case. As a rule, however, preoperative intravenous administration of fluids was carried out in this series (1) when the presence or source of strangulation was not obvious, as in cases of internal hernia or in other cases in which a trial period of conservative therapy was undertaken, (2) when the patient was markedly dehydrated on his admission and (3) when, because of a long-standing obstruction (over 24 hours), the patient's fluid and electrolyte balance demanded correction prior to surgical

15. Eliason, E. L., and Welty, R. F.: A 10 Year Survey of Intestinal Obstruction, Ann. Surg. **125**:57-65, 1947.

intervention. By contrast, the intravenous use of fluids during or after operation was practically universal. In only eight instances the patient did not receive fluids postoperatively, although in 4 of these cases they had been administered during the surgical procedure.

Blood and Plasma.—The indications for the use of blood and plasma are usually fairly well delineated by the condition of the patient. Since an overwhelming number of these operations were undertaken as emergencies the administration of blood was usually reserved for the operative or postoperative period. In only five instances in the entire series was blood given during operation, the indication for its use usually being a state of actual or impending shock. Blood was administered postoperatively in varying amounts in 14 cases. These cases, in general, were either those in which the loop was long and there was evidence of an appreciable blood loss due to the pathologic process or those with postoperative complications. Plasma was administered during operation in seven instances and postoperatively in four.

Antibiotic Therapy.—Experimental work in recent years has emphasized the bacterial source of the toxicity in strangulation obstruction. The experimental contributions to this important phase of pathology and treatment are the products of a long list of careful investigations.[16] It is now well known that if the bacterial factor is controlled adequately the ill effects of strangulation obstruction are greatly diminished. However, as we have pointed out,[6] the bacterial factor is one of many and its control represents an important but not all-inclusive therapeutic advance.

Since 1945 penicillin has been used in every case of strangulation obstruction, representing the last 31 cases in this series. The number of deaths for this group was three, a mortality rate of about 10 per cent.

Evidence as to whether there was improvement in the over-all management of the cases was indicated by dividing our series roughly in half, the first 49 patients representing those treated from 1935 through 1941 and the next 51 those treated from 1942 through 1949 (chart 7). Chemotherapy came into general use in 1942 and was used in most cases in the second group until penicillin became available. Other features of therapy mentioned above undoubtedly also became better understood. Comparison of the two groups revealed that there were eight deaths in the first group and four deaths in the second. Though these figures fall within the chance occurrence of deaths on a statistical basis, all things con-

16. (*a*) Blain, A., III; Kennedy, J. D.; Calihan, R. J., and Harkins, H. N.: Effect of Penicillin in Experimental Intestinal Obstruction: Cure of Strangulated Ileal Obstructions Treated with Penicillin Prior to Late Resections, Arch. Surg. **53**:378-386 (Oct.) 1946. (*b*) Blain, A., III, and Kennedy, J. D.: Effect of Penicillin in Experimental Intestinal Obstructions: Studies on Strangulated Low Ileal Obstructions, Bull. Johns Hopkins Hosp. **79**:1-20, 1946. (*c*) Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: Intestinal Obstruction: II. A Study of the Factors Involved in the Production and Absorption of Toxic Materials from the Intestine, J. Exper. Med. **30**:109, 1919. (*d*) Dragstedt, L. R.; Moorhead, J. J., and Burcky, F. W.: Intestinal Obstruction: An Experimental Study of the Intoxication in Closed Intestinal Loops, ibid **25**:421, 1917. (*e*) Sarnoff, S. J., and Poth, E. J.: Intestinal Obstruction: I. The Protective Action of Succinylsulfathiazole Following Simple Venous Occlusion, Surgery **16**:927-931, 1944. (*f*) Laufman, H.; Martin, W. B.; Method, H.; Tuell, S. W., and Harding, H.: Observations in Strangulation Obstruction: II. The Fate of Sterile Devascularized Intestine in the Peritoneal Cavity, Arch. Surg. **59**:550-564 (Sept.) 1949.

sidered, they do appear to indicate a trend toward improvement of results. This improvement seems to parallel advances in knowledge largely gained in the experimental laboratory and enhanced by clinical experience.

ANALYSIS OF DEATHS

Critical study of the summary of deaths was made to determine which deaths were conceivably avoidable. Postmortem examinations were allowed in only five of the 12 deaths, making it necessary to rely on the clinical impression of the cause of death in seven cases. Of the 12 patients who died, the bowel was replaced in seven. We found that as far as we could tell from our analysis, there were six deaths which might be termed avoidable. Of these, three were due to errors in judging viability or impending perforation and three could be considered surgical errors of other types. The six deaths which we considered as unavoidable were

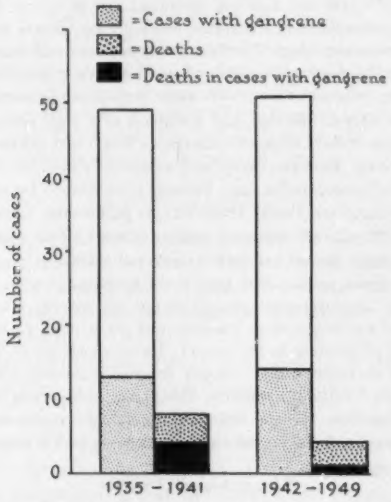

Fig. 7.—Comparison of periods 1935 to 1941 and 1942 to 1949.

due to other complicating disease processes. From a medical point of view at least two cases of postoperative pneumonia might be considered avoidable today. Since the advent of antibiotics, death from postoperative pneumonia is extremely rare. The fact that these deaths occurred in 1936 and 1937 made it necessary to consider them as unavoidable. This consideration also emphasizes the point that the term "unavoidable" is purely relative and may not apply as newer measures of therapy become available. If only the unavoidable deaths had occurred, the mortality rate for this series would have been reduced by half, to 6 per cent (charts 1 and 2).

"AVOIDABLE" DEATHS

CHART 1

CASE 1 (1935).—A 64 year old man had a 64 hour history of inguinal hernia, with 20 cm. of ileum involved. There was bloody peritoneal fluid. The bowel appeared to respond and was replaced, but the patient died on the fourth postoperative day. Autopsy revealed gangrenous bowel, acute peritonitis, bronchopneumonia and pulmonary edema.

CASE 4 (1936).—A 75 year old man had a 48 hour history of femoral hernia. Strangulated ileum and omentum, 30 cm. of discolored bowel and turbid straw-colored fluid were evident. Fifteen centimeters of ileum was resected, after which another 15 cm. appeared cyanotic. This area and the anastomosis were exteriorized. On the fourth postoperative day emesis and signs of intestinal obstruction developed. Treatment consisted of suction and the use of oxygen. The patient died on the fifth day. Autopsy was not performed.

CASE 7 (1938).—A 63 year old man had inguinal hernia; bronchopneumonia was present on his admission, with 7 cm. of ileum black and gangrenous and purulent fluid in the peritoneal cavity. Resection with end to end anastomosis and ileostomy proximal to the anastomosis were performed. Postoperative care included suction and intravenous administration of blood and fluids. Wound disruption occurred on the seventh postoperative day. Conservative treatment was followed by fecal drainage from the wound. The patient died on the twenty-third postoperative day. There was no autopsy, but examination of the operative wound revealed secondary strangulation of a new loop of bowel in the disrupted wound, with perforation of the exposed loop.

CASE 8 (1939).—A 73 year old man had symptoms for 28 hours. Pulmonary emphysema, inguinal hernia and serosanguineous cloudy fluid were present. There was a bluish appearance of the bowel at the constriction rings. The bowel was replaced, and oxygen, suction and fluids were given. He died on the third postoperative day. Postmortem examination revealed perforation in the region of the constriction ring, with acute generalized peritonitis.

CASE 10 (1945).—A 58 year old man had symptoms of a right indirect inguinal hernia for 72 hours. Sixty-seven centimeters of black gangrenous bowel and bloody fluid in the peritoneal cavity were seen. The bowel was exteriorized and a catheter placed into the proximal loop. The patient died on the second postoperative day. Postoperative therapy included suction and administration of penicillin, oxygen and fluids. There was no postmortem examination.

CASE 12 (1949).—A 79 year old man was admitted to the hospital with a three day history of illness. Arteriosclerotic heart disease with dehydration and a femoral hernia were present. There was 12 cm. of dark red ileum, with bloody fluid in the peritoneal cavity. Viability returned, and the hernia was repaired. Postoperative cyanosis in the left leg and a hematoma in the wound were noted. The patient was returned to the operating room after 12 hours for evacuation of the clot and the control of bleeding in the wound. He received 500 cc. of blood, penicillin and suction but died on the operating table. Autopsy revealed focal hemorrhagic infarction of the small intestine, with early localized peritonitis. Hematoma was present in the operative wound, and intraperitoneal hemorrhage, severe bilateral hemorrhagic nephrosis, generalized arteriosclerosis and adenocarcinoma of the prostate with metastases to the lungs were seen.

"UNAVOIDABLE" DEATHS

CHART 2

CASE 2 (1935).[17]—A 50 year old man had a six day history of illness. Coronary heart disease was diagnosed, and there was roentgen ray evidence of complete intestinal obstruction. A paracecal internal hernia, with 36 cm. of black ileum and hemorrhagic and purulent fluid, was present. Resection with end to end anastomosis was performed, and the patient died on the third postoperative day of "bronchopneumonia." Autopsy was not performed.

CASE 3 (1936).[17]—A 77 year old woman had a 48 hour history of illness. She was hypertensive, and rales were heard in both lungs on her admission. A left inguinal hernia with 6 cm. of blue ileum and serosanguineous turbid fluid in the peritoneal cavity were present. The omental mass was amputated and the bowel replaced. On the third postoperative day loud rales were heard in both lungs. The patient died of "bronchopneumonia." Autopsy was not performed.

CASE 5 (1936).—A 79 year old man had a five day history of symptoms. Cardiac decompensation and inguinal hernia were diagnosed, with 20 cm. of ileum involved and serosanguineous

17. The deaths in cases 2 and 3 might be considered avoidable today because of the advent of antibiotics. Since these cases occurred before such drugs were available, they were considered unavoidable for purposes of this paper.

turbid fluid. The bowel appeared to regain viability and was replaced. The patient was cyanotic and dyspneic on the operating table. He received digifolin® and ephedrine but died a half hour after the operation of "heart failure." Autopsy was not performed.

CASE 6 (1936).—A 58 year old man had a duration of symptoms of 72 hours. Inguinal hernia and acute appendicitis were found, with 8 cm. of cyanotic and edematous ileum. The peritoneal fluid was cloudy. Appendectomy and herniorrhaphy were performed; the bowel appeared viable. Postoperative measures consisted of subcutaneous administration of fluids and suction. The patient died on the second postoperative day with "cardiovascular collapse secondary to peritonitis." Autopsy was not performed.

CASE 9 (1942).—A 60 year old woman had symptoms for one week. Diabetes mellitus and ventral hernia were present, with 79 cm. of black gangrenous bowel and serosanguineous turbid fluid in the peritoneal cavity. Bowel resection with end to end anastomosis was performed and sulfanilamide placed in the peritoneal cavity. Postoperative treatment consisted of suction and administration of insulin, fluids and oxygen. The patient died in diabetic acidosis on the sixth day. Postmortem examination revealed pulmonary edema, fibrinous peritonitis and bronchopneumonia.

CASE 11 (1945).—A 64 year old man had benign prostatic hypertrophy and inguinal hernia, with 40 cm. of blue ileum and serosanguineous turbid fluid in the peritoneal cavity. The bowel was replaced, and the patient received penicillin. Urethral obstruction occurred on the fourth postoperative day. Cystoscopy was performed and an indwelling catheter inserted. A febrile course resulted. Suprapubic cystostomy was performed on the twenty-sixth postoperative day, and the patient died four days later with uremia. The clinical diagnosis was pyelonephritis with uremia and cardiac failure and bronchopneumonia. Postmortem examination was not performed.

COMMENT

In cases of incarcerated, nonreducible external hernia with obstructive symptoms, emergency surgical intervention is mandatory as soon as the condition of the patient permits. It is generally not possible to judge which of such incarcerations have become strangulated, and therefore overzealous attempts at reduction by taxis are to be avoided.

When mechanical obstructions due to intra-abdominal disease are being dealt with, the question of strangulation is not always easily answered. The persistence of pain between cramps is an important sign. The roentgenologic picture of a fixed area of distention, a persistently tender, distended abdomen and varying degrees of shock are contributory findings. The inconstancy of these signs, however, has led many surgeons, such as McKittrick and Sarris, for example, to the conclusion that any patient with mechanical obstruction unrelieved by 24 hours of good therapy should be subjected to immediate operation.[1a] This policy, in general, was followed in the present series.

As a result of our study, we feel that the following measures might serve to lower the heretofore reported high mortality rates: (1) elective surgical repair of all uncomplicated hernias; (2) emergency surgical intervention for all complicated external hernias as soon as the condition of the patient permits; (3) judicious employment of adequate supportive care such as suction, parenteral fluid and electrolyte therapy and antibiotic therapy in all cases; (4) the adequate use of blood and plasma when indicated; (5) attention to the dangers of the too protracted use of suction in the presence of mechanical obstruction with continued abdominal pain; (6) resection and primary anastomosis when resuscitative measures leave the least iota of doubt regarding the viability of a released loop; (7) careful examination of the thinned-out portions of bowel at the level of the constriction ring, and (8) avoidance, when possible, of exteriorization procedures.

SUMMARY AND CONCLUSIONS

A study of 100 consecutive cases of intestinal strangulation obstruction due to hernia revealed that certain tangible and clinically measurable factors can be relied on to serve as an index to prognosis and mortality. The group with the highest mortality was the men between the ages of 50 and 79. Though there was no correlation between the duration of symptoms and the presence of gangrene, there was a statistically valid correlation between the duration of symptoms and the mortality. The incidence of strangulation in inguinal hernia is higher than is commonly supposed. The mortality was significantly increased when the involved segment of intestine was long. The character of the sac fluid can serve as a prognostic sign. When it is cloudy or consists of gross blood, one must suspect irreversible damage to the bowel.

The over-all mortality rate for this series was 12 per cent. Errors in judgment of viability occurred in three cases. The mortality rate for resection and primary anastomosis, including deaths from all causes, was 15.8 per cent, a figure considerably lower than those in the literature.

The main features of preoperative and postoperative care which have lowered the mortality rate include the judicious use of suction, parenteral fluid and electrolyte therapy and blood and plasma replacement. Antibiotic therapy has proved to be of inestimable value in reducing toxicity and mortality in this condition. The important contributions of experimental work in this field are cited.

The "unavoidable" mortality rate at present appears to be in the neighborhood of 6 per cent. These figures reflect an improvement in surgical results and indicate that good surgical management can further lower existing mortality rates.

NERVE ANASTOMOSIS IN THE TREATMENT OF FACIAL PARALYSIS

Special Consideration of the Etiologic Role of Total Removal of Tumors of the Acoustic Nerve

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"WHEN a patient desires operative interference for the relief of the deformity, the surgeon should be able to communicate to the patient as accurate a knowledge as possible of the extent of recovery, partial or complete, which the operation offers." This dictum was communicated to Robert Kennedy by Sir Charles Ballance [1] in a discussion of results in spinofacial anastomosis.

We are presenting this survey of 87 cases of unilateral facial paralysis in which spinofacial nerve anastomosis was performed at the Mayo Clinic from Jan. 1, 1926 to Jan. 1, 1949, inclusive. The causative factor for the facial paralysis in 41 cases was the surgical treatment of neurofibroma of the cerebellopontile angle (acoustic neurofibroma), the facial nerve having been injured or sacrificed by necessity in the removal of the tumor. Surgical treatment of mastoid infection accounted for 25 cases and head injury with basal fracture for 7 cases. Surgical interruption of the facial nerve in treatment of facial tic was the cause of the paralysis in 3 cases. An unintentional sacrifice of the seventh nerve in dividing the intracranial portion of the eighth cranial nerve in the treatment of Ménière's disease supplied 2 cases. An anomalous artery of the cerebellopontile angle and a birth injury associated with forceps delivery each accounted for 1 case. The cause was unknown in 7 cases. In 1 of these 7 a pontile glioma developed which was verified three years later at the time of craniotomy. Infection of the mastoid was the probable cause in 2 others.

In 61 of these 87 cases the patients were adequately followed. The analysis of results presented in this paper is based on these 61 cases. In the report of these cases it is our purpose to set forth the expected result of spinofacial nerve anastomosis in the treatment of facial paralysis.

HISTORICAL NOTES

Attack on the facial nerve for the correction of facial paralysis began with the turn of the last century, when Sir Charles Ballance and his associates [2] performed a successful nerve anastomosis employing the spinal accessory nerve. Development

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1. Ballance, C. A.: The Operative Treatment of Chronic Facial Palsy of Peripheral Origin, Brit. M. J. **1**:1288 (May 30) 1903.

2. Ballance, C. A.; Ballance, H. A., and Stewart, P.: Remarks on the Operative Treatment of Chronic Facial Palsy of Peripheral Origin, Brit. M. J. **1**:1009-1013 (May 2) 1903.

was rapid and progressed through the less desirable end to side anastomosis to the correct end to end procedure. The hypoglossal nerve, first used as the donor nerve by Körte,[3] almost simultaneously became a widely used choice, having been favored by Ballance [4] in 1902 within a few years after he began performing nerve anastomosis in cases of facial paralysis. Adson [5] in 1925 reported a representative group from the 30 cases of spinofacial anastomosis performed at the clinic prior to 1925.

Mastoiditis and radical mastoid operations furnished by far the most candidates for the treatment of facial paralysis during the first quarter of this century and continued to do so until the advent of adequate chemotherapy in the late 1930's, when mastoiditis all but disappeared as a disease entity. Trauma and Bell's palsy without spontaneous recovery accounted for the other candidates.

During the last two decades and overlapping with the fading of mastoid surgery, the successful and technically brilliant surgical attack on neurofibromas of the auditory nerve, total removal, has gained favor. Complete removal of the acoustic neurofibroma almost always carried with it sacrifice of the intracranial portion of the seventh nerve.

The early surgical treatment of these angle neurofibromas by finger enucleation carried a mortality rate of about 75 per cent.[6] The development of the intracapsular subtotal removal by Cushing [7] lowered this mortality rate to around 15 per cent, but the recurrence rates in these cases remained high—50 per cent in the four year and five year survivals. The operation of complete removal developed by Dandy [8] now has gained acceptance. Horsley, as mentioned by Tooth,[6c] and Ballance [9] both had successfully effected the total removal of a tumor of the cerebellopontile angle prior to Dandy's accomplishment. In both cases the seventh and fifth cranial nerves were permanently paralyzed. There are acoustic neurofibromas in which only intracapsular removal can be effected, and in some cases it is the procedure of choice. Certainly, permanent injury to the seventh nerve is less likely with

3. Körte, W., and Bernhardt, M.: Ein Fall von Nervenpfropfung des Nervus facialis auf den Nervus hypoglossus, Deutsche med. Wchnschr. **29**:293-295 (April 23) 1903.

4. Ballance, C. A.: A Case of Facial Palsy Treated by Faciohypoglossal Anastomosis in Which an Anastomosis Was Also Made Between the Spinal Accessory and the Distal Segment of the Divided Hypoglossal Nerve in Order to Prevent Permanent Lingual Paralysis and Atrophy, Lancet **1**:1675-1677 (June 12) 1909.

5. Adson, A. W.: Surgical Treatment of Facial Paralysis, Arch. Otolaryng. **2**:217-246 (Sept.) 1925.

6. (*a*) Fumarola, G.: Das Syndrom der Kleinhirnbrückenwinkeltumoren: Klinischer und pathologisch-anatomischer Beitrag, Arch. f. Psychiat. **55**: 781-910 (June) 1915. (*b*) Stewart, T. G., and Holmes, G.: Symptomatology of Cerebellar Tumours: A Study of 40 Cases, Brain **27**:522-591, 1904. (*c*) Tooth, H. H.: The Treatment of Tumors of the Brain and Indications for Operation, in Transactions of the International Congress of Medicine, London, 1913, vol. 11, p. 161.

7. Cushing, H.: (*a*) Concerning the Results of Operations for Brain Tumor, J. A. M. A. **64**:189-195 (Jan. 16) 1915; (*b*) Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontile Angle, Philadelphia, W. B. Saunders Company, 1917; (*c*) Intracranial Tumors: Notes upon a Series of 2,000 Verified Cases, with Surgical-Mortality Percentages Pertaining Thereto, Springfield, Ill., Charles C Thomas, Publisher, 1932.

8. Dandy, W. E.: An Operation for the Total Removal of Cerebellopontine (Acoustic) Tumors, Surg., Gynec. & Obst. **41**:129-148 (Aug.) 1925.

9. Ballance, C. A.: Some Points in the Surgery of the Brain and Its Membranes, London, The Macmillan Company, 1907.

intracapsular removal than with total removal. The sacrifice of the seventh nerve is to be considered in deciding on the type of operation to be applied, and especially is this true in cases with bilateral acoustic tumors (fig. 1). Dandy[10] was able

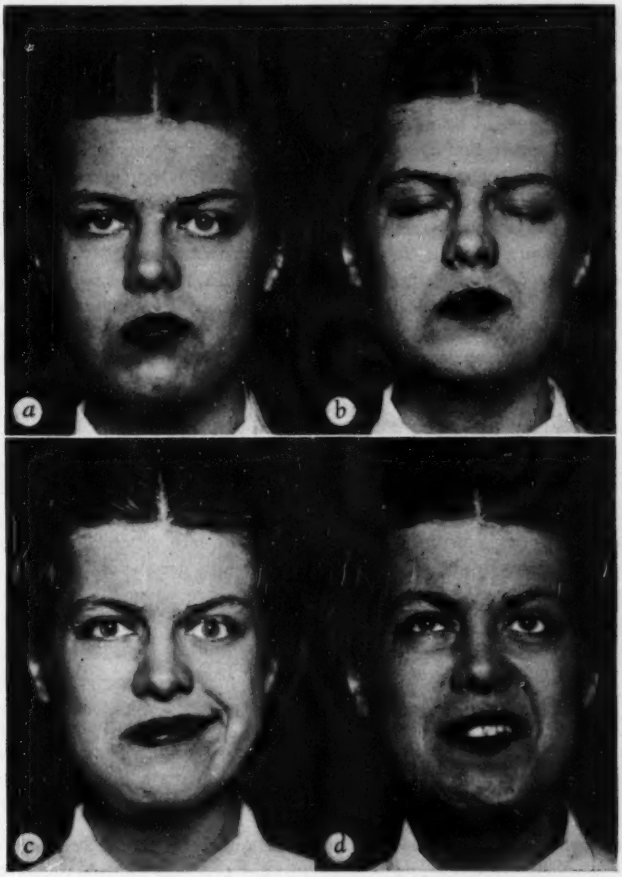

Fig. 1.—Photographs made two and a half years after the complete removal of an acoustic tumor of the right cerebellopontile angle and at the same time an intracapsular removal of a tumor of the left cerebellopontile angle and, fourteen days later, the performance of a right spinofacial anastomosis. The patient was 17 years of age at the time of operation. This patient, a college student, has learned to dissociate the movements of the face. She can contract the orbicularis oculi muscle without moving the other facial muscles. The frontalis muscle contracts when the arm is elevated. (*a*) Face in response; (*b*) ability to close the eyes; (*c*) patient smiling. Note absence of a normal emotional response on the right side, the side of the spinofacial anastomosis. (*d*) Patient showing her teeth. The excellent reinnervation of the right side of the face is obvious.

10. Dandy, W. E.: The Brain, in Walters, W.: Lewis' Practice of Surgery: Clinical Diagnostic, Operative, Postoperative, Hagerstown, Md., W. F. Prior Company, Inc., 1945, vol. 12, chap. 1, pp. 1-671.

to avoid facial paralysis in only one of his large series of total removals, Coleman [11] in one and Peyton and Olson [12] in two. Olivecrona,[13] in a series of 23 total removals, reported anatomic sparing of the seventh nerve in 15 cases; in all but one, however, there was postoperative facial paralysis, according to Nielsen.[14] Frykholm,[15] in a five year follow-up of the cases in which the nerve had been saved, found that only 50 per cent had good function preserved.

Surgeons employing total removal of eighth nerve tumors report better results and less resulting disability than when subtotal removal is employed and no recurrence of the tumor. The sacrifice of the seventh nerve thus remains the chief objection if the operation is technically possible. Attempts are being made to preserve the seventh nerve in total removals.[16] Although an occasional successful feat is reported, it is likely that seventh nerve paralysis will continue to be a common occurrence following total removal of the tumor.

The digression from the subject of spinofacial anastomosis in the foregoing discussion seems desirable, since in our series of cases it was the surgical attack on neurofibromas of the cerebellopontile angle which yielded the most candidates for nerve anastomosis in the correction of the associated facial paralysis since 1935. Of the 64 spinofacial anastomoses performed at the clinic from 1935 to 1949, 41 were carried out subsequent to the removal of an acoustic neurofibroma.

Differing from interruption of the facial nerve within the bony canal, the acoustic neurofibroma and its surgical removal frequently yield homolateral impairment of the fifth cranial nerve or its tract in the brain stem. Involvement of the fifth nerve is second only to that of the eighth nerve in the cardinal signs for diagnostic localization of the acoustic neurofibroma. Some permanent impairment of sensory modalities over the paralyzed side of the face was evident in about one half of our 61 cases.[17] This combination of seventh nerve paralysis and sensory fifth nerve impairment becomes of marked importance when the results of spinofacial anastomosis for the correction of seventh nerve palsy are studied. Much concentrated effort has been applied in the correction of the subsequent paralysis of the seventh nerve, with little or no attention being given to the status of the fifth nerve in the evaluation of the results.

Cushing's early monograph on acoustic nerve tumors [7b] frequently recorded the persistent postoperative impairment of the fifth nerve. Dandy [10] made little mention of the fifth nerve impairment that remained subsequent to his operation of total removal. He did state, however, that a certain amount of trauma always results

11. Coleman, C. C.: Results of Facio-Hypoglossal Anastomosis in the Treatment of Facial Paralysis, Ann. Surg. **111**:958-967 (June) 1940.

12. Peyton, W. T., and Olson, C. K.: Acoustic Neuromas, Bull. Univ. Minnesota Hosp. **19**: 301-314 (Feb.) 1948.

13. Olivecrona, H.: Acoustic Tumors, J. Neurol. & Psychiat. **3**:141-146 (April) 1940.

14. Nielsen, A.: Acoustic Tumors, with Special Reference to End-Results and Sparing of Facial Nerve, Ann. Surg. **115**:849-863, 1942.

15. Frykholm, R.: Treatment of Bilateral Acoustic Tumors: Report of 6 Cases Operated on, with a Review of 13 Cases from the Literature, Acta chir. Scandinav. **92**:451-469, 1945.

16. Cairns, H.: Acoustic Neurinoma of Right Cerebello-Pontine Angle: Complete Removal; Spontaneous Recovery from Post-Operative Facial Palsy, Proc. Roy. Soc. Med. **25**:35-40, 1931. Olivecrona.[13]

17. This does not include those cases with corneal anesthesia as the only evidence of fifth nerve impairment.

to the fifth nerve, the trauma rarely being sufficient to produce more than a slightly impaired sensation in the face. This impairment, he agreed, is enough to cause a high incidence of trophic keratitis. No reference was made to its possible effect on the results of the subsequent spinofacial anastomosis.

Olivecrona [13] reported on total removals of acoustic neurofibromas, stressing the anatomic sparing of the seventh nerve. Frykholm,[15] in reporting a five year follow-up on these cases, stressed the occurrence of functional sparing of the seventh nerve. Neither author made mention of the incidence of permanent involvement of the fifth nerve. Frykholm included in his report the results of eight spinofacial anatomoses performed subsequent to removal of the angle tumor. Seven of the patients had satisfactory recovery of facial "tonus." One had no recovery. Nielsen [14] made a general statement concerning the expected results of spinofacial anastomosis performed after total or subtotal removal of the acoustic neurofibroma in 29 cases. "The main effect of an anastomosis is abolition of atrophy of the facial muscles and restoration of tonus. Facial movements are not restored but at least the eye can be closed by moving the shoulder." We wonder what deductions could be drawn from a more specific investigation of the amount of functional recovery seen in these cases and whether or not accompanying fifth nerve impairment was frequent and, if so, what effect it had on the ultimate result.

Although Ballance brought the operative procedure of anastomosing nerves in the treatment of facial paralysis into favor, Kennedy [18] gave the first and still outstanding clinical observation and follow-up on the progress and recovery of function subsequent to spinofacial anastomosis. The results in his case were as satisfactory as could be hoped for today. His patient regained function in all portions of the face, including the forehead, and was able to dissociate movements to a great extent. When the arm was raised, however, mass contracture of the face always occurred. Emotional and reflex responses on the affected side of the face, of course, were lacking. Noticeable asymmetry was still evident. A phenomenon mentioned by Kennedy and by Cushing [19] separately, and later noticed by others, was the occurrence of movement in the eyelid within a few days or a week subsequent to anastomosis. This still needs adequate explanation. It is certain that this early movement is not a sign of regeneration, as Kennedy thought. Sherrington's hypothesis of reciprocal innervation, as Cushing suggested, is still possibly the best explanation. This would attribute the motion to relaxation of the elevator of the upper lid.

An excellent review by Adson [5] concerning the history of surgery of facial paralysis and the pros and cons in the choice of the spinal accessory or the hypoglossal nerve as the donor nerve needs few supplementary remarks. Attention has been brought to the frequent impairment of the fifth cranial nerve in acoustic neurofibromas and their surgical removal. It has been noted by others [20] and seems

18. Kennedy, R.: Junction of the Peripheral Segment of the Divided Facial Nerve with the Trunk of the Spinal Accessory Nerve for the Treatment of Facial Spasm in a Woman, Phil. Tr. Roy. Soc. London **194**:152-162, 1901.

19. Cushing, H.: The Surgical Treatment of Facial Paralysis by Nerve Anastomosis, with Report of a Successful Case, Ann. Surg. **37**:641-659, 1903.

20. Poppen, J. L.: Facial Paralysis Following Complete Extirpation of Acoustic Neuromas: Treatment and Results in 17 Patients, Lahey Clin. Bull. **1**:8-14 (March) 1939.

likely to us that the choice of the twelfth nerve would be less desirable in these cases. Impairment of the seventh, fifth and twelfth cranial nerves would seem to be more disabling and disturbing to the patient, especially in such necessary functions as mastication and speaking, than impairment of the seventh, fifth and eleventh cranial nerves.

PROCEDURE AND MATERIAL

Reiteration of the definitive points of the procedure performed in anastomosing the spinal accessory nerve with the facial nerve is unnecessary. The success of the anastomosis depends on accurate approximation of the nerve ends, with sufficient relaxation of each contributing stump to prevent tension. In compliance with these criteria, occasionally the anastomosis was performed superficial to the posterior belly of the digastric muscle rather than beneath it.

Additional procedures were carried out in 30 of the 87 anastomoses. The superior cervical sympathetic ganglion was sectioned and resutured in some cases. In 19 cases a second anastomosis was performed by interrupting the descendens hypoglossi and joining its central end to the distal portion of the severed spinal accessory nerve. In 9 of these 19 cases the superior cervical sympathetic ganglion also was sectioned.

The attack on the cervical sympathetic nerves was designed by Leriche [21] as a treatment for lagophthalmos. By producing Horner's syndrome on the paralyzed side of the face, the asymmetry in the width of the palpebral fissures may be lessened. The anastomosis of the descendens hypoglossi and the remaining portion of the spinal accessory nerve was suggested by Grant.[22] He carried out this additional procedure to combat the otherwise expected atrophy of the trapezius and sternocleidomastoid muscles. Craig [23] utilized the suggestions of Leriche and Grant and employed both of these additional procedures in some of the cases which are included in our series.

The results, however, in the cases with these additional procedures were not sufficiently different from the results of the routine spinofacial anastomosis alone to enable one to draw conclusions as to their effectiveness.

Local infiltration with piperocaine hydrochloride (metycaine hydrochloride®) or procaine hydrochloride is our choice of anesthetic agent. When local anesthesia is utilized, the time necessary between total removal of a tumor of the cerebellopontile angle and the performance of spinofacial anastomosis is reduced to a minimum and consequently the period of hospitalization is shorter than if a general anesthetic agent were employed. Two patients complained of moderately severe pain when the spinal accessory nerve was manipulated and cut. The pain was localized mainly to the back of the head. The spinal accessory nerve is purely a motor nerve, and its terminations are not in the region in which the pain was localized. It is logical to assume that in these 2 patients sensory fibers from the

21. Leriche, R.: A propos de traitement de la lagophtalmie par l'ablation du ganglion cervical supérieur, Bull. et mém. Soc. nat. de chir. **52**:948, 1926.

22. Grant, W. W.: Traumatic Facial Paralysis: Anastomosis of Facial Nerve to Spinal Accessory and the Peripheral End of Accessory to the Descendens Hypoglossi, J. A. M. A. **55**:1438-1442 (Oct. 22) 1910.

23. Craig, W. M.: Facial Paralysis and Its Surgical Treatment, S. Clin. North America **17**:1093-1101 (Aug.) 1937.

cervical plexus were coursing cephalad in close approximation with the trunk of the spinal accessory nerve and that the pain was initiated by stimulation of these fibers when the nerve was handled and cut.

Blepharorrhaphy was performed for protection of the cornea in 15 of the 17 cases in which there was impairment of the fifth cranial nerve and in 4 others. This was done at the time of anastomosis or early in the postoperative period. The blepharorrhaphy was released when recovery of facial movement was adequate to protect the eye. There was no case presenting bilateral facial paralysis in this series of 87 cases. The age range was from 3½ to 64 years. The majority of the patients were in the fifth and sixth decades of life, with only nine in the first and four in the seventh decade. Forty-four males and 43 females comprised the group, the side of the lesion being about equally distributed (43 right and 44 left).

An adequate follow-up was accomplished in 61 of the 87 cases. In the other 26, either insufficient information was received or the follow-up covered a period of less than six months. Study of the 61 cases continued for an average of approxi-

Fig. 2.—Photographs made sixteen months after the complete removal of a tumor of the left cerebellopontile angle and, ten days later, the performance of a left spinofacial anastomosis. The patient was a colonel in the Greek Army at the time of operation and was 48 years of age. The photographs were sent from Athens. (*a*) Face in repose; (*b*) incomplete ability to close the left eyelids. This function probably will improve, since the patient is intelligent and cooperative. (*c*) Lack of emotional response on the left side when the patient smiles.

mately two years postoperatively, varying from six months to six years and three months.

RESULTS

The results shown in the table reveal excellent function in 30 cases, good in 20, fair in 8 and failure in 3. The grading of results into excellent, good, fair and failure was a logical one and not absolute. By establishing certain criteria as a basis for each group, different degrees of recovery were represented. An excellent result consisted in movement in the upper and lower portion of the face, the muscular strength being about 75 per cent of normal. Effective closure of the eyelids was the usual performance. Frontalis motion may be noted. A good result revealed an almost straight mouth and good motion in the lower part of the face. The upper part of the face usually demonstrated motion, but muscular contractions were weak and insufficient in closing the eyelids (fig. 2). A fair recovery

represented improvement in muscular tone of the paralyzed side of the face, which lessened the asymmetry. Slight motion was evident in the lower portion of the face.

The accompanying table represents the results in the 61 cases of spinofacial anastomosis according to extent of cranial nerve involvement, etiologic mechanism for the involvement and the time elapsed from the onset of the paralysis until anastomosis was effected. Significant difference is noted in the results of the cases that presented, in addition to the seventh and eighth cranial nerve impairment, impairment of the fifth cranial nerve. Twenty-six of the 43 cases having normal sensation over the face obtained an excellent result, 12 good and 4 fair. There was 1 failure. Of the 18 cases in which impairment of the fifth nerve was evident in

Results in Sixty-One Cases of Unilateral Facial Paralysis in Which Spinofacial Nerve Anastomosis Was Performed

Cranial Nerve Palsy	Etiology	Time Elapsed Before Anastomosis	Results				
			Excellent	Good	Fair	Failure	Total
VIII, VII	Acoustic neurofibroma, removal	1 wk. to 6 mo.	9	6	1	0	16
	Head injury	6 mo.; 1 yr., 1 mo.	0	2	0	0	2
	Anomalous artery of pontile angle	1 yr.	1	0	0	0	1
	Section of nerve for Ménière's disease	4 mo.	0	1	0	0	1
	Unknown	5 mo.	0	0	0	1	1
	Totals		10	9	1	1	21
VII	Mastoid surgery	6 mo. to 7 yr.	13	3	3	0	19
	Facial neurectomy for tic	0	2	0	0	0	2
	Unknown	5 mo.	1	0	0	0	1
	Totals		16	3	3	0	22
VIII, VII, V	Acoustic neurofibroma, removal	1 wk. to 1 yr., 10 mo.	4	8	3	2	17
VIII, VII, V, VI, II	Head injury	1 yr.	0	0	1	0	1
	Totals		4	8	4	2	18

a test of the modalities of sensation over the face, 4 secured an excellent result, 8 a good result and 4 a fair result. Two showed no evidence of recovery. The comparison of results in these two groups demonstrates a decided difference. One may conclude that any significant degree of anesthesia over the paralyzed side of the face is an obstacle to obtaining the best possible functional result from spinofacial anastomosis.

The lapse of time between onset of the paralysis and nerve anastomosis seemed to have little effect on the expected result, especially if the operation was performed within six months of onset. Although a representative number of cases in which the paralysis existed for years is lacking, in one case of our series in which there was facial palsy of seven years' duration the result of spinofacial anastomosis was excellent. Trumble [24] also minimized the effect of the duration of the facial

24. Trumble, H. C.: Nerve Anastomosis in the Treatment of Facial Paralysis, Australian & New Zealand J. Surg. **17**:297-299 (April) 1948.

palsy in his series of hypoglossofacial anastomosis. This factor certainly seems to be less important than it is in nerve surgery of the extremities, in which atrophy and contracture modify the result.

Atrophy of the paralyzed side of the face was evident in only 12 of the 61 cases. It was of mild or moderate degree and never severe. The recovery in these 12 cases with atrophy was considered excellent in 3, good in 6 and fair in 3. This seems to imply that the existence of atrophy indicates diminished ability to have a good functional recovery.

Clinical evidence of reinnervation of the frontalis muscle was noted in slightly more than one fourth of the cases in this series. In only one case was this muscle observed to obtain normal strength; in the others paresis and incoordinated contraction were observed. The neurofibroma group of 33 cases in which there was adequate follow-up furnished an interesting comparison in respect to recovery of the frontalis muscle. Six of 16 cases (38 per cent) having no involvement of the fifth cranial nerve revealed function in the frontalis muscle; yet in only 1 of 17 (6 per cent) with involvement of the fifth nerve was movement in this muscle accomplished.

Although 11 of the 61 adequately followed patients with spinofacial anastomosis had some symptom referred to the shoulder on the involved side, subsequent to operation the symptom persisted longer than six to ten months postoperatively in only 3 of these. The symptom was usually aching and difficulty in elevation of the arm. Atrophy of the shoulder was variable. In many cases no atrophy could be detected, and rarely was it severe. One patient, however, was returned to the clinic by his local physician with a tentative diagnosis of tumor of the shoulder. This turned out to be only a prominent coracoid process accentuated by the atrophy.

The climax of achievement in these patients is the accomplishment of dissociated movement, this being attained to a satisfactory degree by only 7 of our 61 patients.

LIMITATIONS IN THE SURGICAL TREATMENT OF FACIAL PALSY

There are limitations to the degree of recovery to be expected after surgical repair of the facial nerve. Residual dysfunction is almost always evident regardless of whether decompression, resuturing or grafting has been the operation performed.[25] The maximal recovery or near perfect result leaves much to be desired. Some of the residuals are asymmetry, failure of reinnervation of the frontalis muscle, faulty reinnervation giving rise to associated and mass movements and failure of return of emotional and reflex responses. Asymmetry, frontalis paresis or paralysis and evidence of faulty reinnervation are frequently observed as residuals even after spontaneous recovery in cases of neuropathy of facial nerve (Bell's palsy). They are consistently observed in the resuturing or grafting procedure.

25. (*a*) Ballance, C. A., and Duel, A. B.: Operative Treatment of Facial Palsy by Introduction of Nerve Grafts into Fallopian Canal and by Other Intratemporal Methods, Arch. Otolaryng. **15**:1-70 (Jan.) 1932. (*b*) Bunnell, S.: Surgical Repair of the Facial Nerve, ibid. **25**:235-259 (March) 1937. (*c*) Collier, J.: Facial Paralysis and Its Operative Treatment, Lancet **2**: 91-94 (July 27) 1940. (*d*) Duel, A. B.: Clinical Presentation of Improvement in Surgical Repair of the Facial Nerve, Laryngoscope **44**:599-611 (Aug.) 1934. (*e*) Ford, F. R., and Woodhall, B.: Phenomena Due to Misdirection of Regenerating Fibers of Cranial, Spinal and Autonomic Nerves, Arch. Surg. **36**:480-496 (March) 1938. Coleman.[11]

Faulty reinnervation is inevitable on the basis of the anatomic and physiologic processes in regeneration of nerves.[25e] There is sufficient evidence that the number of regenerating fibers may exceed the number formerly present in the intact nerve. The regenerating fibers do not always choose the channels that they occupied prior to interruption. It is reasonable to assume that misdirection of regenerating fibers into the terminal branches of a peripheral nerve is an occurrence to be expected. The clinical observations of mass contractions, faulty contractions and associated movements are the results of this faulty innervation with misdirected fibers. The desired impulse thus can be shunted, yielding poverty of intentional motion along with undesired contractions in other muscles. Curious observations are recorded in the literature [26]; for instance, in the early stages of recovery when the patient is asked to show his teeth, no movement is seen, but when he is asked to close an eye, the angle of the mouth is drawn up. Recovery proceeds as reinnervation becomes more complete. At a later time mass movements are more likely to obscure the isolated associated dysfunction. Spiller [27] was the first to offer faulty regeneration as the explanation for some of these abnormal facial movements. In so doing, he contradicted a former hypothesis which attributed the phenomena to a change in the state of the seventh nerve nucleus.

The numerous muscles innervated by the facial nerve blend themselves into a complexity of contractions and relaxations yielding a variety of facial expressions. The complete relaxation of the muscular action of a side of the face seen in unilateral paralysis gives rise to an expression of despair on this side. The contracture of the frontalis muscle raises the eyebrow as in surprise. The contraction of the orbicularis oculi at the same time as relaxation of the frontalis and the levator palpebrae superioris closes the eyelid.

A normal facial nerve was stimulated by a tetanizing current. The stimulating electrode was placed near the trunk of the facial nerve high in the fossa between the ramus of the mandible and the mastoid process. On stimulation, massive unilateral contraction of the muscles of the face occurred. The appearance of the face was similar to the contraction initiated on shoulder motion in a patient demonstrating an excellent result from a spinofacial anastomosis. No wrinkling of the brow was noted. It seems logical to us from this observation that the strength of the orbicularis oculi muscle overrides that of the frontalis muscle. Thus, if we accept such reasoning based on this inadequate observation, we have a theoretical explanation for a common discrepancy seen in the results of the spinofacial anastomosis. This explanation is not entirely acceptable, for the occasional electromyographic studies made on patients who had undergone the anastomosis frequently yielded no evidence of frontalis reinnervation.

Another point to be considered when reasoning as to why reinnervation of the lower part of the face seems consistently more adequate than that in the upper part possibly concerns the problem of atrophy. As mentioned in our results, atrophy of the face was described in only about one fifth of the 61 cases. It is certainly more difficult to discern and evaluate than that in extremities with a spinal nerve

26. Morris, W. M.: Surgical Treatment of Facial Paralysis: A Review of 46 Cases, Lancet **2**:558-561 (Sept. 2) 1939.

27. Spiller, W. G.: Contracture Occurring in Partial Recovery from Paralysis of the Facial Nerve and Other Nerves, Arch. Neurol. & Psychiat. **1**:564-566 (May) 1919.

injury. Is it possible that the continued passive motion which the lower facial muscles receive through the more or less constant use of the jaw in talking, chewing and other actions predisposes to their successful recovery of function? The muscles of the upper part of the face are deprived of this intense physical therapy. It is more probable that both of the foregoing explanations for the discrepancy of functional recovery existing between the upper and lower portions of the face share in its cause.

The ability of the patient with a spinofacial anastomosis to improve beyond the stage of mere mass contraction of the reinnervated facial muscles, as in conquering any physical disability, depends on his age, intelligent insight and willing cooperation. After the surgical procedure of spinofacial anastomosis was accomplished, the patient was instructed to massage the paralyzed side of his face and to practice in front of a mirror, initiating facial movement through moving the shoulder. He was told that the asymmetry of the face would lessen after about three months and that movement could be expected within three to six months. He was also informed that suppression of facial expression on the normal side would render his deformity less obvious to others.

From the study of this series of cases much evidence accumulated to substantiate the belief that only the exceptional patient is able to apply these instructions on his own in such a way as to obtain the maximal benefit of the operation. Placing all the patients in the care of physicians qualified in physical medicine for a period when reinnervation has occurred should enhance the results of this operation, especially in reference to dissociation of movements.

The deficit in emotional and reflex responses, of course, is permanent. Dissociation of movement in closing the eyelid without massive contraction of the entire side of the face is occasionally observed. Dissociation of shoulder-face movement should be accomplished by the majority rather than by a few.

Sensory impairment over the paralyzed side of the face is an additional handicap altering the desired result of nerve anastomosis, as shown in the comparison of results in the table. In the present era the tumor of the cerebellopontile angle and its surgical treatment appear to be the commoner cause for paralysis of the seventh cranial nerve. Consideration of the status of the fifth cranial nerve must be included before communicating to the patient the extent of recovery to be expected subsequent to spinofacial anastomosis.

SUMMARY

A follow-up study of 61 of 87 patients who underwent nerve anastomosis for unilateral facial palsy is presented. The results have reassured us that whenever possible the spinal accessory nerve should be employed to conduct impulses to the facial musculature in cases in which reestablishment of the continuity of the facial nerve is impossible. Although perfect function cannot be expected, particularly in regard to emotional responses, the nerve anastomosis does offer satisfactory reinnervation in the majority of cases.

Evidence was obtained from this study to show that the duration of the facial palsy is not as important a consideration in the selection of candidates for spinofacial anastomosis as has been previously thought. Definite atrophy of the facial muscles, on the other hand, militates against a good functional recovery.

Consideration of the status of the fifth cranial nerve in cases in which a tumor of the cerebellopontile angle has been removed is important in predicting the expected result of spinofacial anastomosis. When a patient with a benign tumor of the cerebellopontile angle, particularly with a neurofibroma of the eighth cranial nerve, presents himself for treatment, complete removal of the tumor is desirable even though it means sacrificing the seventh cranial nerve. The residual dysfunction of a spinofacial anastomosis is a small price to pay for a cure of a brain tumor that otherwise might cause the death of the patient.

Undesirable symptoms involving the shoulder from utilizing the spinal accessory nerve are almost never observed. It should go without saying that no good can be accomplished unless the spinal accessory nerve was intact and functioning normally prior to the anastomosis with the facial nerve.

The most successful surgical anastomosis will fail to give a good functional result unless the patient is intelligent, cooperative and willing to practice conscientiously in striving to dissociate shoulder and facial movement.

DERMATOFIBROSARCOMA PROTUBERANS

A Report of Thirty-Nine Cases

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DARIER and Ferrand [1] in 1924 described an unusual progressive and recurring tumor of the skin of fibromatous or fibrosarcomatous character. One year later Hoffmann [2] reported several similar cases and coined the neologism, "dermatofibrosarcoma protuberans." The neoplasm is rare, but it must have been seen and treated, though unidentified, many years before its recognition as a tumor entity. In earlier years at the Memorial Hospital it was erroneously considered to be a dermal neurosarcoma of low grade malignancy.

Our present study is based on a series of 39 such tumors confirmed by histological study and collected during a 20 year period between January 1929 and January 1949 at the Memorial Hospital. Thirty patients have been constantly available for follow-up observations, but nine were lost for subsequent appraisal. An analysis of these nine delinquent patients confirms the accepted opinion of good results following surgical treatment: A 52 year old man exhibited no recurrence when last seen three years after treatment; a 42 year old man had no evidence of tumor when last seen three years after treatment; one patient died of ocular melanoma eight and a half years after the dermatofibrosarcoma was excised; two men aged 20 and 42 years when last seen two years after treatment were without evidence of recurrence; an 87 year old woman when last seen was without recurrence one and one-third years after treatment; a 41 year old woman was lost to observation within six months after therapy; one man refused secondary treatment for a tumor recurrent after a year, and there was one operative death involving a 41 year old man, presumably due to anesthesia.

CLINICAL HISTORY

The disease has a remarkably uniform clinical history. The patient, usually a middle-aged adult, presents himself with a growth which is painless but which has been slowly increasing in size for a number of years. Sometimes the first manifestation is reputed to be a flat, reddish blue or purple mark on the skin at birth or in early childhood. Years later a small nodule appears in the cutis and

From the Memorial Center for Cancer and Allied Diseases, New York.

1. Darier, J., and Ferrand, M.: Dermatofibromes progressifs et récidivants ou fibrosarcomes de la peau, Ann. de dermat. et syph. **5**:545-570, 1924.

2. Hoffmann, E.: Über das knollentreibende Fibrosarkom der Haut (Dermatofibrosarkoma protuberans), Dermat. Ztschr. **43**:1-28, 1925.

hypoderm at this identical site and slowly begins its growth. More commonly the neoplasm appears spontaneously as a pea-sized cutaneous nodule in early adult life. The duration of the tumor before the patient seeks medical attention is generally long.

Having made its appearance, the small intracutaneous nodularity slowly increases in size by expansile growth, and if more than one nodule develops, they eventually fuse to form a dense fibrotic plaque. This elevated plaque remains confined to the dermis and the subcutaneous tissues and spreads horizontally as it invades these tissues in an infiltrative manner. The underlying fascia and muscle are seldom involved except as a late complication of recurrent tumors.

After a varying period, usually from one to four years, there appears on the surface of the fibrotic plaque one or more projecting nodular masses. Once they appear, growth of the tumor proceeds more rapidly, and it may enlarge to the size of a man's fist within a few weeks or months. The bosslike projections may occur as hemispherical sessile tumors or more rarely have the appearance of a pedunculated mushroom-like growth. In its early stage the entire lesion is firm and dense. The overlying skin, which is always fixed to the tumor, assumes a bluish red or purple discoloration and, as the tumor enlarges, becomes thinned and atrophic. This atrophy may reach such a degree that the least trauma, such as the friction of overlying clothes, may be sufficient to cause the surface to bleed and produce superficial ulceration. Once ulcerated, the growth may fungate through as a mass of reddish brown granulomatous-like tissue, at which stage it is often soft.

SYNONYMS

In a collective review of the literature it is evident that these tumors, identical in type and possessing a similar clinical picture, course and microscopic appearance, have been variously designated by the numerous authors interested in this neoplastic entity. The following names have been given to the neoplasm: (*a*) dermatofibrosarcoma protuberans (Hoffmann); (*b*) sarcomatous tumors resembling keloid (R. W. Taylor); (*c*) hypertrophic morphea (Sherwell); (*d*) progressive recurring dermatofibroma (Darier and Ferrand); (*e*) fibrosarcomatous tumors with attenuated dermal surfaces (Hertzler); (*f*) sarcomatoid fibroma of the skin (McMaster), and (*g*) fibrosarcoma of skin (Stout).

HISTORICAL REVIEW

The earliest description of this disease was published in 1890 by Taylor,[3] who described a nodular, lobulated, intracutaneous tumor present for 15 years on the left shoulder of a 43 year old man. The clinical and histological description of the lesion corresponds exactly with the tumor under discussion. It was locally excised four times, with recurrence following each procedure. The fifth attempt was a wide surgical excision; after this extirpation the patient was unavailable for observation.

3. Taylor, R. W.: Sarcomatous Tumors Resembling in Some Respects Keloid, J. Cutan. & Genito-Urin. Dis. **8**:384-387, 1890.

Binkley [4] has introduced a case report culled from the collection of the Central Bureau for the Study of Tumors. The patient was first seen professionally in 1890 with a cutaneous nodule 1 cm. in diameter situated on the anterior abdominal wall. It grew to a diameter of 15 cm. before it was excised in 1896. From 1912 to 1928 the patient underwent four operations for successive recurrences. He finally died of metastatic sarcoma on Sept. 2, 1928, 38 years subsequent to the known onset.

Sherwell [5] presented a patient before the New York Dermatological Society in 1890, with the tentative diagnosis of "hypertrophic morphoea."

In 1903 Johnston [6] reported the case of an indolent intracutaneous tumor of 20 years' duration on the shoulder of a middle-aged man. It was excised *in toto*. There were no metastases. The author concluded that it was a slowly growing fibroblastic tumor of low grade malignancy and having a tendency to recur if incompletely excised. He advocated wide surgical excision. A study of the clinical appearance, microscopic changes and course of this neoplasm establishes it as a definite example of dermatofibrosarcoma protuberans.

Kuznitsky and Grabisch [7] in 1921 published three case reports of these tumors originating on the chest wall.

It was not until Darier and Ferrand [1] published their classical article on this subject in 1924 that the tumor finally became established as a clinicopathological entity. They reported four cases at that time and added a fifth one in the ensuing year.[8] In the original article, Darier made the statement that these growths had a tendency to occur on the anterior abdominal wall because in four patients the tumors were found either close to the umbilicus or adjacent to the groin. It has since been shown that although the abdominal wall is one of the favorite sites for occurrence it is by no means the only one, and indeed it has developed practically everywhere on the body. Darier quoted only a single bibliographic reference in which a similar tumor was described, namely, Professor Unna's [9] book, "Histopathology of Skin Diseases" (1894), the location in this instance being juxtaumbilical. Darier, perhaps in his enthusiasm to announce his independent discovery and because of his mistaken belief that the tumors arose primarily from the abdominal wall, neglected to study the references to more or less identical neoplasms occurring on other parts of the body. His thesis was otherwise thorough and authoritative; in fact, the neoplasm was subsequently referred to as Darier's recurring fibroma of the skin.

Hoffmann [2] in 1925 published three cases from his own experience and suggested the term "lump-producing fibrosarcoma of the skin" or dermatofibrosarcoma protuberans. Hoffmann gave priority to Coenen,[10] who in 1909 reported two

4. Binkley, G. W.: Dermatofibrosarcoma Protuberans: Report of 6 Cases, Arch. Dermat. & Syph. **40**:578-594 (July) 1939.

5. Sherwell, S.: Morphoea, J. Cutan. & Genito-Urin. Dis. **8**:72-73, 1890.

6. Johnston, J. C.: Fibrosarcoma Cutis, J. Cutan. & Genito-Urin. Dis. **21**:23-26, 1903.

7. Kuznitsky, E., and Grabisch, A.: Über myxomatöse Fibrosarkome der vorderen Brustwand, Arch. f. Dermat. u. Syph. **131**:24-32, 1921.

8. Darier, J.: Un nouveau cas de fibrosarcomes de la peau, opéré guerin, Bull. Soc. franç. dermat. et syph. **33**:32, 1926.

9. Unna, P. G.: Histopathology of the Diseases of the Skin, translated by N. Walker, New York, The Macmillan Company, 1896.

10. Coenen, H.: Granulationsgeschwülste und Sarkome, Beitr. z. klin. Chir. **63**:337-346, 1909.

dermal fibrosarcomas. In his article Hoffmann made a detailed bibliographic study of this neoplastic disease. Including his three patients, Hoffmann summarized a total of 15 published case reports, fulfilling the criteria which he considered pathognomonic of this condition. He included three case reports of Kartscher [11] and three of Pfeiffer [12] as typical examples of dermatofibrosarcoma protuberans, although those authors considered their reported neoplasms to be variants of desmoid tumors and were of the opinion that they arose from the superficial fascia and not from the skin. However, the tumors in each of these six cases were said to have remained confined to the skin and the subcutaneous tissues and were freely movable on their under surfaces.

After the publications of Darier and Hoffmann the recognition of this tumor as a specific neoplastic entity was generally accepted. Pathologists as a whole did not classify it within the group of desmomas, fibromas or fibrosarcomas originating from fascia, muscle or tendon sheaths.

THEORIES OF ORIGIN; HISTOGENESIS

(a) Parasitic Theory.—Darier originally attributed the onset of the tumor to the supposed local action of some unknown parasite.

(b) Traumatic Origin.—Traumas have frequently been mentioned as possibly influential in the production of this growth. Persistent irritation by a button is mentioned by Hoffmann as a presumptive cause of the tumor which developed on the volar aspect of the wrist. Sylvestre Begnis and Picena [13] observed the development of dermatofibrosarcoma protuberans in the scar of a human bite on a male breast. In Hoffmann's review of 39 cases collected from the literature and his own case, trauma was alleged to have preceded the initial appearance of the tumor in eight instances. In our series of 39 patients a history of injury to the site on which the tumor arose was given by five patients (13 per cent). On the basis of this percentage, the traumatic relationship would seem to be only coincidental. It could have served to attract the patient's attention to a previously existing mass. Again it could have served as a "trigger mechanism" in stimulating the neoplasm to appear in a person already predisposed to its development by a desmoplastic diathesis. We concluded that injury as an etiological factor played no significant role in our series of cases. It could well be that some of the remaining patients had long since forgotten any specific blow or injury to the affected area. We shall cite the five examples of reputed trauma. 1. A 55 year old man sustained a hammer blow to the sacral region and the tumor developed after a few weeks. 2. A 47 year old man fell against a machine, injuring the pectoral region, and the neoplasm appeared three months later. 3. A 74 year old woman after an interval of 39 years discovered the tumor growing in the scar of an abdominal operation. 4. In a 34 year old professional boxer the tumor occurred on the right upper chest

11. Kartscher, J. A.: Erfahrungen über desmoide Geschwülste der Bauchdecken in den Jahren 1880-1903, Inaug. Dissert., Breslau, 1904, cited by Hoffmann.[2]

12. Pfeiffer, C.: Die Desmoide der Bauchdecken und ihre Prognose, Beitr. z. klin. Chir. **44**:334-401, 1904, cited by Hoffmann.[2]

13. Sylvestre Begnis, C., and Picena, J. P.: Fibrosarcoma de Darier sobre cicatriz por mordisco, Rev. méd. de Rosario **36**:233-239, 1946.

wall, the site of repeated bruises. 5. A 45 year old woman had a growth on the skin of the right upper abdominal wall, where she experienced pressure from her corset.

(c) Hereditary Influence.—There was no evidence of familial occurrence.

(d) Mammogenic Theory.—Kuznitsky entertained the hypothesis that the tumors were probably misplaced embryonic remnants of breast tissue; in his three cases the growth occurred on the chest wall. The histological appearance does not support this contention. More recently, Binkley favored Kuznitsky's theory. He made a spot map of the body showing the locations of dermatofibrosarcoma protuberans in reported cases. The majority of the lesions were situated on the anterior surface to the right or left of the midline, either adjacent to or on the mammary ridge. It was his assumption, therefore, that the tumors arise from embryonic breast tissue along the mammary ridge. It is difficult to reconcile this conception with their occurence on the wrist, penis, head, back and lower extremities as shown in the regional distribution in our cases.

(e) Neurogenic Theory.—In 1929 Mosto [14] introduced his theory of the neurogenic origin, contending that the tumors developed from the supportive tissue of the nerves or from nerve tissue proper. He designated the lesions as dermatoneuromas or dermatoschwannomas. Undoubtedly the cellular structure in some regions does suggest the diagnosis of neurofibroma or neurogenic sarcoma. However, in the various case reports no mention is made of the tumor occurring within a nerve trunk or requiring anatomic dissection from a nerve. Special tissue stains have not substantiated the theory that the tumors originate in the sheath of Schwann. Finally, in no reported case has there been evidence of associated cutaneous neurofibromas or von Recklinghausen's disease either fully developed or in forme fruste.

(f) Angiomatous Theory.—Hoffmann suggested the possibility of the derivation of the tumors from blood vessels, as he was impressed by the presence of enlarged, lacunar, thin-walled blood vessels. In many instances the vessels were represented only by a single layer of endothelial cells, with the remainder of the wall being replaced by the fibrosarcoma-like tissue. The possible relationship of this tumor to the sclerosing hemangiomas of Gross and Wolbach [15] has been noted by several observers. Some pathologists consider them to be one and the same lesion, and indeed under the microscope it may be impossible to differentiate them. There are, however, certain definite differences. The sclerosing hemangiomas are said to occur chiefly on the extremities, whereas dermatofibrosarcoma is distributed more commonly on the trunk. In their incipiency, both neoplasms may appear as firm, intracutaneous nodules, but the sclerosing hemangioma is usually single, measures a few millimeters to 1 cm. in diameter and is not characteristically reddened. The sclerosing hemangiomas are featured microscopically by the presence of large numbers of phagocytes containing hemosiderin and vacuolated foam cells filled with

14. Mosto, D.: Sobre una nueva interpretación de los dermatofibromas de Darier, Semana méd. **1**:855-859, 1929.

15. Gross, R. E., and Wolbach, S. B.: Sclerosing Hemangiomas: Their Relationship to Dermatofibroma, Histiocytoma, Xanthoma and to Certain Pigmented Lesions of the Skin, Am. J. Path. **19**:533-551, 1943.

lipid substances interspersed among many fine capillaries and the connective tissue framework of the tumor. Stout [16] emphasizes the fact that the neoplasm known as dermatofibrosarcoma protuberans does not characteristically show the large number of foam cells or phagocytic cells containing blood pigment and that when these cells are present they are coincidental and not integrate portions of the tumor.

(g) Fibroblastic Theory.—By the use of Masson's trichome or Mallory's connective tissue stain, it now becomes practically certain that the basic structure of this neoplasm is the fibroblast or connective tissue cell. The tumor essentially must be considered to be a fibromatous or fibrosarcomatous tumor, similar histopathologically to the other desmoplastic tumors of divers types but distinguished clinically by its location, appearance and manner of growth.

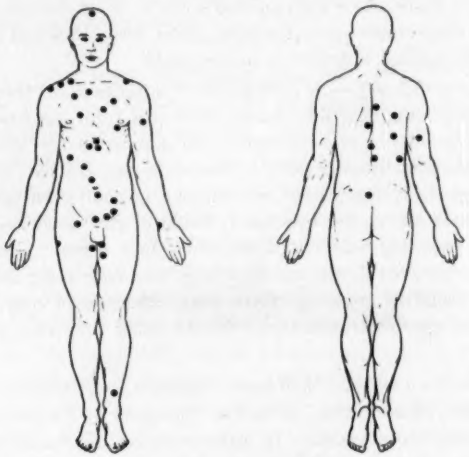

Fig. 1.—Regional distribution of dermatofibrosarcoma protuberans.

INCIDENCE OF DERMATOFIBROSARCOMA PROTUBERANS

The tumor is neither rare nor common. The majority of published reports are based on only one to six personally treated lesions. In 1926 Hertzler [17] reported a total of 26 cases which he had accumulated from experience with more than 5,000 tumors during a quarter of a century. Stout collected 29 cases from the Laboratory of Surgical Pathology of Columbia University during the 40 year period from 1907 to 1946. The 39 case reports from the Memorial Hospital constitute the largest series on record and are of more than average value because the tumors were treated on a single surgical service by the same surgical staff. More than 50,000 patients with tumors enrolled in the institution during this period, and therefore the incidence in our experience is slightly less than 0.1 per cent.

16. Stout, A. P.: Fibrosarcoma: The Malignant Tumor of Fibroblasts, Cancer **1**:30-67, 1948.

17. Hertzler, A. E.: Fibrosarcomatous Tumors of the Skin of the Trunk, Characterized by Attenuated Dermal Surfaces, Ann. Surg. **84**:489-496, 1926.

Fig. 2.—Dermatofibrosarcoma of scalp.

Fig. 3.—Dermatofibrosarcoma of trunk. *A*, left pectoral region; *B*, right supramammary region; *C*, suprapubic region.

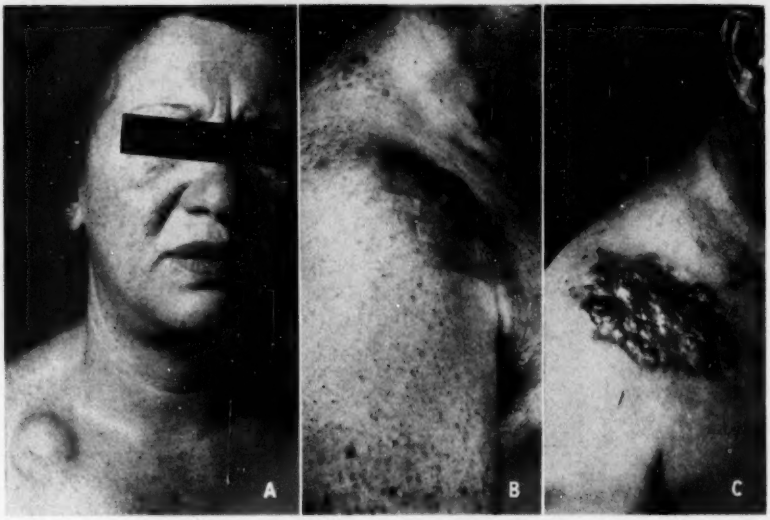

Fig. 4.—Dermatofibrosarcoma of shoulder. *A*, right clavicular region; *B*, right pectoral region; *C*, right anterior shoulder region.

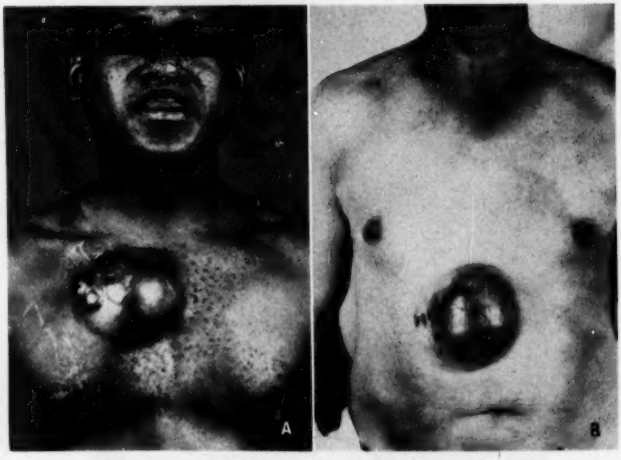

Fig. 5.—Dermatofibrosarcoma protuberans of anterior trunk. *A*, right parasternal region; *B*, epigastrium.

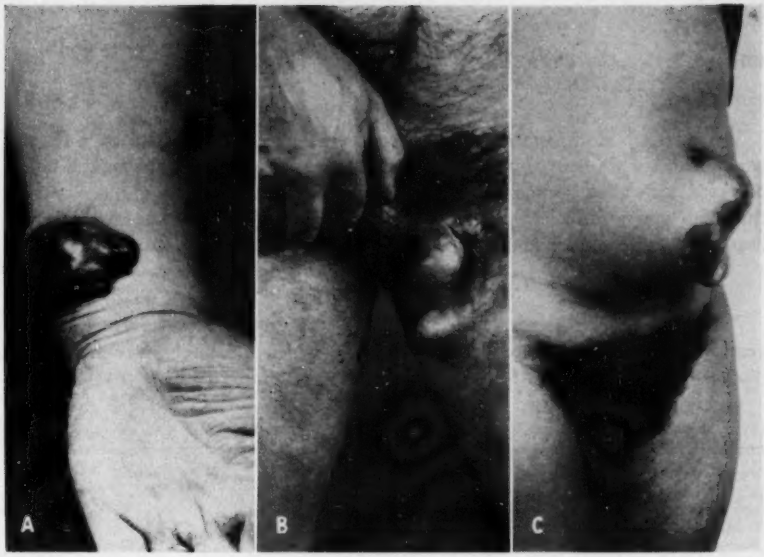

Fig. 6.—Clinical examples of dermatofibrosarcoma protuberans. *A*, volar aspect of left wrist; *B*, left femoral trigone; *C*, infraumbilical region.

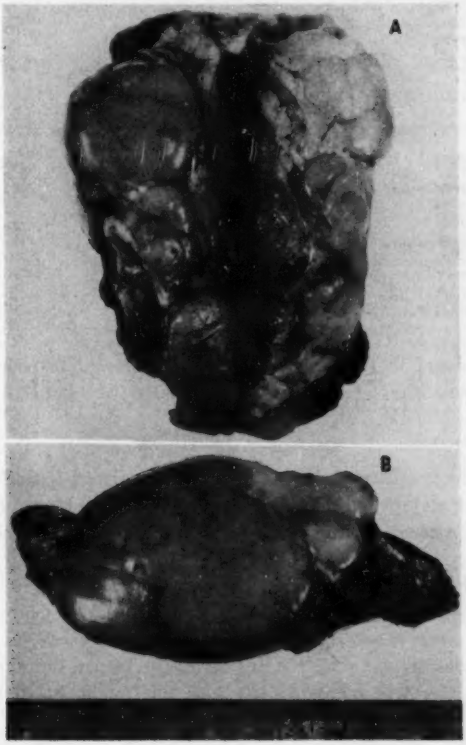

Fig. 7.—Gross specimens of dermatofibrosarcoma protuberans. Note pseudoencapsulation and smooth uniform texture.

REGIONAL DISTRIBUTION

As noted by Hoffmann and others, the tumor has a greater predilection for the trunk than for the extremities. An analysis of our cases showed that the lesion occurred with almost equal frequency on the chest, back, abdomen, upper part of the thigh and groin (table 1). Infrequently the neoplasms are situated on the head, scalp, extremities and genitals.

AGE AND SEX DISTRIBUTION

The age of our patients varied from 14 to 87 years, with an average of 44.3 years, which corresponds to the decennium in which the tumor was most often discovered, namely, 41 to 50 years (table 2). Of our 39 patients, 24 (61.5 per

TABLE 1.—*Location of the Tumor*

Location	Number of Cases
Sacrum and back	8
Chest	7
Upper part of thigh and groin	7
Abdomen	5
Supraclavicular region and shoulder	4
Epigastric region	3
Upper part of arm	2
Wrist	1
Lower part of leg	1
Scalp	1

TABLE 2.—*Age Distribution*

Age, Yr.	Number of Cases
11-20	3
21-30	1
31-40	9
41-50	15
51-60	7
61-70	1
71-80	2
Over 80	1

cent) were males and 15 (38.5 per cent) were females. This sex ratio is almost identical with the figures of Hoffmann, viz., 13 males (61.9 per cent) and 8 females (38.1 per cent).

SIZE OF THE TUMOR

The size of the neoplasms when first seen by us varied from 0.5 to 20 cm. in diameter, with the majority in the larger-sized group. The largest tumor measured 21 by 15 cm. and was composed of many agminated confluent nodules.

RATE OF GROWTH AND DURATION OF SYMPTOMS

The rate of growth is imperceptibly slow at first, even many years elapsing before the tumor starts to enlarge with increasing rapidity in weeks or months until it may attain a considerable size. In our series the known duration of the tumor before medical advice was sought varied from one month to 49 years, although

in half the cases the patients applied for treatment in one to five years after the lesions were first noticed. The history of long duration of the tumor emphasizes

TABLE 3.—*Duration of the Disease Before First Medical Treatment*

Duration of Disease	No. of Cases
A. Lesion present since birth	4
B. Lesion present over 30 yr. and excluding A	2
C. Lesion present between 21-30 yr.	1
D. Lesion present between 11-20 yr.	5
E. Lesion present between 6-10 yr.	2
F. Lesion present between 1-5 yr.	19
G. Lesion present less than 1 yr.	6

TABLE 4.—*Cases Collected from the Literature by Hoffmann*

	Author	Sex Age	Trauma	Location of Lesion	Duration, yr.	Treatment	End Results
1.	Kartscher [11]	M 71	0	Abdomen	60	Excised thrice	Died of pneumonia after 3d excision
2.	Kartscher	M 55	+	Abdomen	6	Excised thrice	No evidence of disease, 14 mo.
3.	Kartscher	F 55	0	Abdomen	7	Excised thrice	Not stated
4.	Pfeiffer [12]	F 61	0	Abdomen	31	Excised thrice	Not stated
5.	Pfeiffer	M 21	0	Abdomen	15	Excised twice	No evidence of disease, 2 yr. after last treatment
6.	Pfeiffer	F 53	+	Abdomen	2	Excised twice	Not stated
7.	Coenen [10]	F 61	0	Right shoulder	10	Excised twice	No evidence of disease, 3 yr.
8.	Coenen	M 53	0	Abdomen	27	Excised twice	No evidence of disease, 8 yr.
9.	Arzt, L.: Arch. f. Dermat. u. Syph. 115: 18, 1912	F 45	0	Above left breast	15	Excised twice	Not stated
10.	Kuznitsky [7]	F 43	+	Right clavicle	25	Excised twice	Recurred in 5 yr.
11.	Kuznitsky	F 38	+	Right breast	15	Excised twice	Not stated
12.	Kuznitsky	M 22	0	Left chest	15	Excised twice	No evidence of disease, 2 yr.
13.	Darier [1]	M 48	0	Abdomen	3	Multiple and varied treatment over 16 yr. with recurrence each time	Died of pneumonia
14.	Darier	M 67	0	Inguinal region	42	Multiple and varied treatment over 35 yr. with recurrence each time	Died of gangrene of leg
15.	Darier	F 43	0	Inguinal region	4	Excision	Not stated
16.	Darier	M 42	0	Abdomen	9	Roentgen ray	Temporarily regressed but recurred
17.	Lutz: Schweiz. med. Wchnschr. 3: 571, 1922	M 32	0	Left loin	9	Excision	Not stated
18.	Weidman, F. D.: Arch. Dermat. & Syph. 5: 421 (March) 1922	M 20	0	Upper thigh	7	X-ray and excision	Not stated
19.	Hoffmann	M 57	0	Right buttock	12	Excision	No evidence of disease, 2½ yr.
20.	Hoffmann	M 60	+	Right wrist	50	Excision	No evidence of disease, 1 yr.
21.	Hoffmann	M 49	0	Subscapular region	3	Excision	No evidence of disease, 1 yr.

its relative slowness of growth. In one of Hoffmann's patients the tumor had existed for 50 years; in one of Darier's the duration was 42 years, and in two of our group the tumors had been present for more than 30 years. In four of our

patients the lesions were present at birth. In them it originated either as a small raised nodule which manifested growth tendencies in later years of life or else was present as a small bluish red flat stain in the skin beneath which a small tumor gradually appeared and grew during the ensuing years. These case histories of congenital dermatofibrosarcoma protuberans may be summarized as follows: (*a*) a 35 year old man had the tumor in the abdominal skin; it had grown rapidly for one year; (*b*) a 33 year old woman had the tumor in the epigastrium; it had grown rapidly for one year; (*c*) a 49 year old woman had the tumor overlying the sternum; it had grown rapidly for six months; (*d*) a 42 year old man had the tumor in the right femoral trigone; it had grown rapidly for two years.

GROSS ANATOMIC STRUCTURE

The growth manifests itself on the skin surface as a single or as multiple nodules which are adherent to the overlying skin but which generally remain freely movable on the underlying fascia. In our series all were firmly attached to the skin, and the majority were confined to the dermis and the subcutaneous tissue. The tumor develops usually from a single point of genesis, but multicentric origin has occurred. The nodules may be sessile or pedunculated. The later conglomerate tumors have a corrugated or cobblestone appearance. The epidermis is stretched thinly over the tumor but may be stripped from it. The shiny translucent appearance of parts of the tumor may be due to myxomatous changes occasionally found. In 32 of our 39 cases the skin over the tumors was discolored, the color varying from a pale pink or red to a bluish red or purple; in seven patients the superjacent skin was a normal color. In time, minute erosions of the skin occur, and later the exopathic tumor protrudes through the skin as a bleeding tomato red mass. The intact tumor is firm, but the fungating, infected, edematous tumor may be soft and pulpy. On cut section the lesion is ligneous and resistant and composed of a glistening grayish white homogenous tissue which may be red and hemorrhagic at its core. The appearance of encapsulation is due to a condensation of fibrous tumor tissue at the periphery. The growth separates easily from the fascia as a rule, because it seldom invades the subjacent fascia or muscle. The neoplasm infiltrates on a horizontal plane through the corium and the subcutaneous fat. The proclivity of the tumor to extend in fine linear projections well beyond the apparent margins is responsible, no doubt, for the common surgical error of too limited, conservative excision and subsequent regrowth of residual tumor. Kuznitsky reported one case in which the lesion had infiltrated the pectoralis major muscle. In our series of 39 cases there were only five instances in which the underlying fascia and muscle were infiltrated by dermatofibrosarcoma protuberans. These unusual case reports concerned the following patients: (*a*) an 87 year old woman in whom the recurrent tumor invaded muscles of the arm; (*b*) a 45 year old woman in whom the tumor invaded the anterior rectus sheath; (*c*) a 35 year old man in whom the tumor invaded the anterior rectus sheath; (*d*) a 42 year old man in whom the recurrent tumor invaded the fascia over the latissimus dorsi muscle, and (*e*) a 63 year old woman in whom the recurrent tumor invaded the deep epigastric fascia. Invasion of muscle and fascia by recurrent dermatofibrosarcoma is readily understood. The slow growth of the tumor probably explains why the fascia and muscles are not invaded sooner, but, as with other neoplasms possessing infiltrating

capabilities, it would appear that with sufficient time the adjacent structures would be ultimately invaded in all cases.

HISTOLOGICAL STRUCTURE OF THE TUMOR

The microscopic appearance of the dermatofibrosarcoma protuberans is essentially that of a cellular fibroma which in some regions bears a close resemblance to a well differentiated fibrosarcoma of low grade malignancy. The histological structure is not uniform throughout any one tumor or in any group of these neoplasms, as it may vary from dense collagenous tissue with few cells to a cellular fibroma and, as stated before, ultimately to its most anaplastic expression, a well differentiated fibrosarcoma. It has been previously noted that the diagnosis of dermatofibrosarcoma protuberans as a neoplastic entity is more readily made on the basis of the clinical history and appearance than it is on microscopic examination,

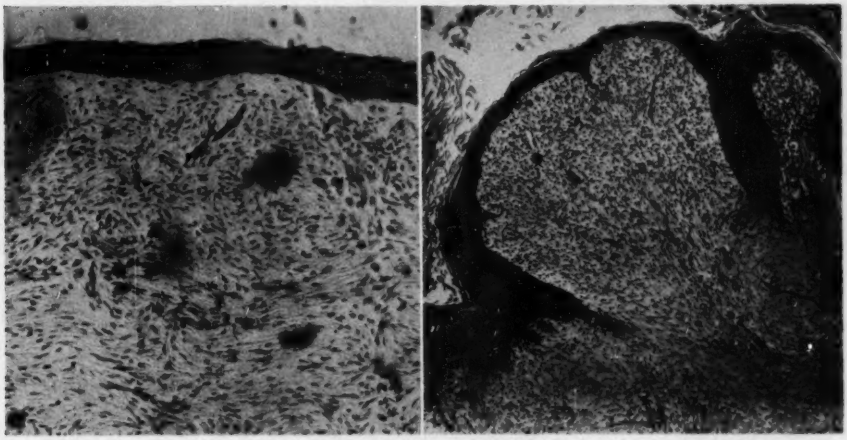

Fig. 8.—Photomicrographs of dermatofibrosarcoma protuberans. The fibromatous lesion is within the corium. The epidermis or scarf skin is attenuated over the surface of the neoplasm.

inasmuch as the histological features are so similar in all the desmoplastic tumors. The growth originates in the dermis, and as it develops it encroaches on the papillae, causing them to become compressed and finally to disappear. Because the tumor begins in the corium, it is naturally adherent to the epidermis, which becomes attenuated over the larger nodules and may rupture, leaving an ulcerated surface. The epidermal accessories such as the sweat glands, oil glands and hair follicles atrophy and disappear. Fine fibrillary projections of the tumor extend subjacent to it and invade the subcutaneous fat lobules. The microscope reveals that the circumscription of the lesion is by a pseudocapsule of condensed fibrous tissue.

The cellular portions of the neoplasm are made up of fusiform or spindle-shaped cells arranged in whorls or bundles sometimes around a fine central capillary or lacunar vessel. Both Darier and Hoffmann recognized the presence of large lacunar blood vessels within the tumor, a finding so constant that Hoffmann postulated the angiomatous origin of the neoplasm. These vascular lacunas are lined by a single

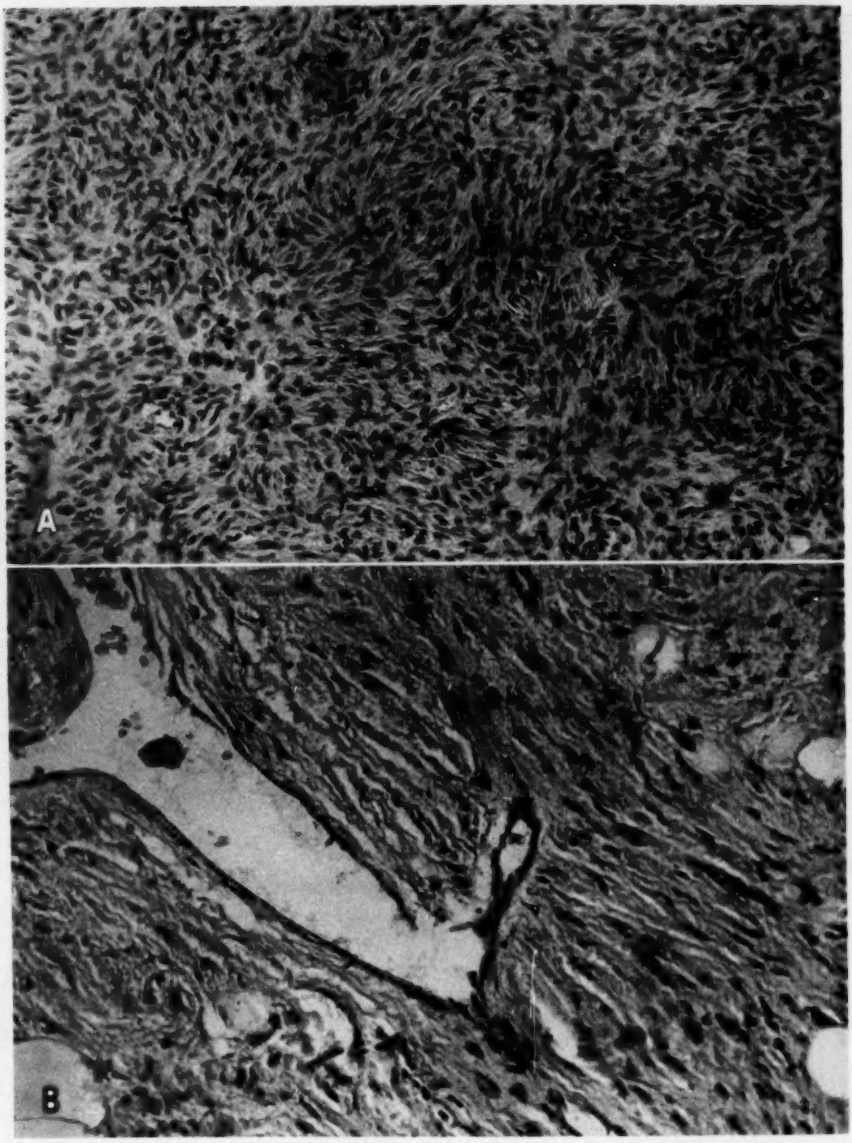

Fig. 9.—*A*, compact interlacing whorls of neoplastic connective tissue. *B*, the fibrous element of the tumor appears to rest directly or perivascularly on the endothelial lining of the vessels as it does in some sclerosing angiomas.

layer of endothelial cells resting directly on an investment of fibromatous tumor tissue. As would be expected, the more cellular portions of the tumor occur in the actively growing segments, usually the peripheral nodules; per contra, the less cellular and more fibrous portions are in the hard sclerotic and older plaques. The frequency of mitoses varies according to the cellularity and rapidity of growth of the various parts of the tumor but, as a rule, mitotic figures are rare. Large areas of myxomatous and hyaline degeneration are seen. Although the microscopic picture may strongly resemble neurofibroma because of the interlacing fibrils, special stains enable one to identify the cells as fibroblasts and the interlacing cells as of connective tissue origin. Mallory's connective tissue stain may be employed to demonstrate the collagenic stroma. Because hemorrhage and deposition of hemosiderin has occurred within the tumor, the inexperienced pathologist has been known to confuse this lesion with melanoma.

IS DERMATOFIBROSARCOMA PROTUBERANS MALIGNANT? DOES IT METASTASIZE?

The frightening aspect of the well developed tumor, its notorious tendency to recur locally after excision and the erroneous interpretation of its microscopic features have contributed to an early opinion that it was malignant. The term "dermatofibrosarcoma protuberans" fortunately is a misnomer, because the majority of these neoplasms do not metastasize. It has been thought to be malignant because of its known tendency for local recurrence after a presumably wide excision; the logical explanation of this complication is an unintentional and unsuspected incomplete initial removal. In our 39 patients there has not been a single instance of metastasis to regional lymph nodes or viscera. It may be, however, that if we follow our patients for a long time, especially those who relate successive episodes of local recurrence, some instances of metastasis may occur to prove an exception to our opinion and experience.

From a review of the literature, it would appear that metastasis to lymph nodes and viscera is rare but has occurred. This tumor is said to behave more after the fashion of fibrosarcoma and metastasize more frequently through the blood stream than through the lymphatic vessels. In Darier's first case a separate nodule developed at a distance of 13 cm. from the original lesion. Although Darier did not excise this second nodule for pathological study, he nevertheless concluded that it represented a secondary metastatic tumor inasmuch as it had a clinical appearance identical to that of the original lesion. He based his assumption of metastases on the fact that the skin between the original and secondary tumors felt normal. We know this conclusion is not valid because microscopic infiltration within the dermis is possible over such a distance. In his second patient a secondary lesion developed at a distance of 10 cm. from the original one; it was excised, but the skin between the two lesions was never removed and examined for evidence of infiltration. These tumors may have been of multicentric origin. Arthur Purdy Stout did not report a single instance of metastasis occurring in his group of 29 cases. Bezecny [18] in 1933 reported that one of his three patients with dermatofibrosarcoma protuberans died of pulmonary metastases, and Sciacchitano [19] in 1935 also related his experience

18. Bezecny, R.: Lungmetastasen beim Dermatofibrosarcoma protuberans, Arch. f. Dermat. u. Syph. **169**:347-353, 1933.

19. Sciacchitano, G.: Sopra un caso di fibro-sarcoma cutaneo con metastasi polmonari, Tumori **9**:427-438, 1935.

TABLE 5.—*Cases of Dermatofibrosarcoma Protube*

		History				Physical Findings					
Case	Sex, Age	Pain	History of Trauma	Duration to First Treatment	Duration to Treatment Here	Size, Cm.	Location	Color	Deep Infiltration	Bleeding	Ulceration
1	M 55	Mild occasional	Yes	3 yr.	5 yr.	2.5 × 4	Sacral region	Pink	—	No	No
2	M 44	No	No	6 mo.	1 yr.	0.6 in diameter	Left upper arm	Red	—	No	No
3	F 41	No	No	12 yr.	12 yr.	4.5 in diameter	Right infraclavicular region	Normal	—	No	No
4	M 47	No	Yes	1 yr.	1 yr.	2.5 in diameter	Right chest	Pink	—	No	No
5	F 74	No	Operative scar 19 yr. ago	1 yr.	2 yr.	13 × 4 × 2 high	Left lower abdomen	Purplish red	—	No	No
6	M 54	Shooting pain	No	2½ yr.	3 yr.	3 × 2 × 1	Left upper chest	Brownish yellow	—	No	No
7	M 34	Tender 2 mo.	Yes; boxer	1 yr.	4 yr.	17 × 12 × 4	Right upper chest	Dark pink	—	No	No
8	M 43	No	No	1 yr.	1 yr.	3 in diameter	Right back	Red	—	Yes	Yes
9	F 87	No	No	1½ yr.	3 yr.	9 × 6	Middle third of right arm	Red	Yes	No	No
10	F 30	No	No	10 yr.	12 yr.	10 × 6	Left sacral region	Dark brown	—	Following slight trauma	No
11	M 34	No	No	8 yr.	8 yr.	2 × 2	Lateral right thigh	Dusky red	—	No	No
12	M 59	No	No	2 yr.	2 yr.	5 × 5	Anterior right shoulder	Purplish red	—	No	No
13	F 38	No	No	4 yr. approximately	30 yr. approximately	6 × 6	Volar surface, right wrist	Red	—	On trauma	No
14	M 54	No	No	1 mo.	10 yr.	10 × 8	Left upper chest	Pink to red	—	No	No
15	M 36	No	No	1 yr.	14 yr.	10 × 5	Left back	Red	—	No	No
16	F 45	No	Pressure from corset 18 yr.	18 yr.	18 yr.	4 × 3	Right upper abdomen	Bluish pink	Yes	No	No
17	M 48	No	No	2 yr.	3½ yr.	9 × 7	Left midback	Light pink	—	No	No
18	F 42	During menses	No	5 mo.	1 yr. 10 mo.	8 × 6	Left groin	Red	—	No	No
19	M 35	Burning 3 wk	No	Since birth	35 yr.	12 × 7 × 5	Right upper abdomen	Purplish red	Yes	No	No
20	M 80	No	No	1 mo.	1 mo.	6 × 3 × 3	Left groin	Normal	—	No	No
21	F 33	No	No	Many yr. (33 ?)	33 yr.	5 × 4	Epigastric region	Brownish	—	No	No
22	F 43	No	No	1 yr. approximately	3 yr.	4 × 3 × 2	Upper, inner left thigh	Red	—	No	No
23	M 46	No	No	2 mo.	2 yr., 4 mo.	5 in diameter	Left supraclavicular region	Bluish	—	No	No
24	M 52	No	No	17 yr.	17 yr.	6 × 5	Right lower chest	Normal to light pink	—	No	No
25	M 35	No	No	1 yr.	1 yr.	5 × 4	Right scapula	Normal	—	No	No
26	M 42	No	No	1 yr.	26 yr.	10 × 4 × 4	Lower back	Light brown	Yes	No	No
27	F 49	No	No	Born with red mark, began to grow as small tumor	6 mo.	1.5 × 1	Epigastric region	Red	—	No	No
28	F 14	No	No	2½ yr.	3 yr.	0.5 in diameter	Anterior left lower leg	Normal	—	No	No
29	M 57	Yes 2 wk.	No	15 yr.	15 yr.	6 × 5	Mid upper back	Pale pink	—	No	Yes
30	F 63	No	No	1 yr.	23 yr.	4.5 in diameter	Epigastric region	Normal	Yes	No	No

* No previous treatment was carried out in cases 3, 4, 5, 12, 16, 19, 20, 21, 22, 24, 25, 27, 29, 31, 33, 34, 37 and 38 and no treatment at the Memorial Center in case 10.

rans at the Memorial Cancer Center, New York

Provisional Diagnosis at the Memorial Center	Previous Treatment *				Treatment at the Memorial Center *				End Results
	Excision Only	Irradiation Only	Excision, Irradiation	Recurrence After First Treatment	Excision Only	Excision, Irradiation	Recurrence After Treatment Here and Further Treatment	Skin Grafting	
Neurogenic sarcoma	+	..	..	2 yr.	..	+	None	No	No evidence of disease 19 yr., 7 mo.
Neurogenic sarcoma	..	..	+	4 mo.	..	+	None	No	Died 8 yr., 5 mo. from malignant melanoma
Neurofibroma	..	..	..	.....	..	+	None	No	No evidence of disease 10 yr.
Infectious granuloma	..	..	..	.....	..	+	4 yr.; wide excision	No	No evidence of disease 4 yr., 9 mo.
Neurogenic sarcoma	..	..	..	.....	..	+	None	No	No evidence of disease 8 yr., 7 mo.
Cancer developing in sebaceous cyst	..	+	..	Lesion persisted	+	..	None	No	No evidence of disease 6 yr., 5 mo.
Liposarcoma	+	..	..	3 mo.	+	..	None	Yes	No evidence of disease 5 yr.
Dermatofibrosarcoma protuberans	Cautery excision	..	..	Lesion not destroyed	+	..	None	No	No evidence of disease 5 yr., 2 mo.
Deferred	..	+	..	2 yr.	..	+	None	No	No evidence of disease 1 yr., 3 mo.; final
Neurofibroma	+	..	..	None	..	..	.....	...	No evidence of disease 5 yr., 2 mo.; patient treated elsewhere
Dermatofibrosarcoma protuberans	+	..	..	Incompletely excised	+	..	None	No	No evidence of disease 4 yr., 8 mo.
Cancer developing in sebaceous cyst	..	..	..	.....	+	..	None	No	No evidence of disease 4 yr., 10 mo.
Dermatofibrosarcoma protuberans	+	..	..	3 wk.	+	..	None	Yes	No evidence of disease 4 yr., 7 mo.
Dermatofibrosarcoma protuberans	+	..	..	1 yr.	+	..	None	Yes	No evidence of disease 3 yr., 4 mo.
Dermatofibrosarcoma protuberans	..	..	+	9 yr.	+	..	20 mo.; wide excision	Yes	No evidence of disease 1 yr., 8 mo.
Sclerosing hemangioma	..	..	..	.....	+	..	None	No	No evidence of disease 3 yr., 6 mo.
Neurogenic sarcoma	(1)	..	..	7 mo.	+	..	None	No	No evidence of disease 1 yr., 7 mo.
	(2)	..	..	9 mo.					
Neurogenic sarcoma	+	..	..	5 mo.	+	..	None	No	No evidence of disease 1 yr., 2 mo.
Deferred	..	..	..	.....	+	..	None	No	No evidence of disease 1 yr.
Metastatic melanoma	..	..	..	.....	+	..	None	No	No evidence of disease 6 mo.
Deferred	..	..	..	.....	+	..	None	No	No evidence of disease 1 mo.
Papilloma ?	..	..	..	1 yr.	+	..	1 mo.; wide excision	No	No evidence of disease 1 mo.
Spindle cell sarcoma	(1)	..	(3)	1) 6 mo.	+	..	2 yr. 8 mo.	Yes	No evidence of disease 1 yr., 2 mo.
	(2)	..	..	2) 1 yr.			2 yr.		
	..	..	..	3) 3 mo.			Wide excision		
Deferred	..	..	..	.....	+	..	None	No	No evidence of disease 3 yr.
Dermatofibrosarcoma protuberans	..	..	..	.....	+	..	None	Yes	No evidence of disease 4 yr., 3 mo.
Neurofibroma	+	..	..	14 yr.	+	..	None	Yes	No evidence of disease 4 yr., 9 mo.
Sclerosing hemangioma	..	..	..	.....	+	..	None	No	No evidence of disease 3 yr., 3 mo.
Dermatofibrosarcoma protuberans	+	..	..	5 mo.	+	..	None	No	No evidence of disease 6 mo.
Dermatofibrosarcoma protuberans	..	..	..	.....	+	..	None	Yes	No evidence of disease 2 yr., 5 mo.
Desmoid tumor	(1)	..	..	12 yr.	+	..	None	No	No evidence of disease 2 yr., 3 mo.
	(2)	..	..	4 yr.					
	(3)	..	..	7 yr.					

TABLE 5.—*Cases of Dermatofibrosarcoma Protub*

		History				Physical Findings					
Case	Sex, Age	Pain	History of Trauma	Duration to First Treatment	Duration to Treatment Here	Size, Cm.	Location	Color	Deep Infiltration	Bleeding	Ulceration
31	M 59	No	No	33 yr.	33 yr.	11 × 10 × 8	Right shoulder	Purplish red	—	No	Yes
32	M 42	No	No	Several months	18 yr.	6 × 4	Left chest	Red	—	No	No
33	M 42	No	No	35 yr. approximately	35 yr.	12 × 8 × 5	Right femoral region	Pale pink	—	Yes	No
34	F 27	After standing long	No	Since early childhood	25 yr. ?	4 × 3	Right upper thigh	Pink	—	No	No
35	M 20	No	No	5 yr.	7 yr.	5 × 3	Left lower abdomen	Red	—	No	No
36	M 34	No	No	1 yr.	2 yr.	20 × 15	Upper inner left thigh	Red	—	No	No
37	F 18	No	No	2 yr.	2 yr.	10 × 6	Right supraclavicular region	Bluish red	—	No	No
38	F 41	No	No	32 yr.	32 yr.	8 × 6	Lower midabdomen	Dark pink	—	No	No
39	M 41	No	No	1 yr.	23 yr.	21 × 15	Scalp	Normal	Yes	No	No

with one case of dermal fibrosarcoma which metastasized to the lungs. In Binkley's report of six cases of dermatofibrosarcoma protuberans published in 1939, he stated that his first patient, in whom five excisions for local recurrences had been made, finally died of metastases 32 years after the original operation. Gaté [20] in 1948 described an instance of splenic metastasis from a tumor of this type. Hertzler spoke of these tumors as metastasizing via the lymphatic vessels and reported on lymph node dissections. We believe that he sometimes confused this tumor with nonpigmented malignant melanoma.

SYMPTOMATOLOGY

The symptom of pain was elicited from seven of our 39 patients, and in none of them was it ever severe or incapacitating. The pain was usually of a "shooting" or "burning" character and did not persist for a prolonged time. In one patient, it was present only during her menstrual period. Pain is certainly not a feature of this neoplastic disease, and in fact the lack of severe pain is more characteristic. In some instances the patient may experience discomfort by reason of the location of the lesion or its size or because of some injury to it. In only four patients was there a history of bleeding from the tumor; this hemorrhage was of a minor nature only and usually occurred after trauma. Dermatofibrosarcoma protuberans does not affect the general health of the patient, which possibly accounts for the common delay in the institution of treatment.

20. Gaté, J.; Croizat, and Coudert, J.: Métastase splénique probable d'un fibrosarcome de Darier et Ferrand, Lyon méd. **179**:40, 1948.

erans at the Memorial Cancer Center, New York.—Continued

Provisional Diagnosis at the Memorial Center	Previous Treatment *				Treatment at the Memorial Center *				End Results
	Excision Only	Irradiation Only	Excision, Irradiation	Recurrence After First Treatment	Excision Only	Excision, Irradiation	Recurrence After Treatment Here and Further Treatment	Skin Grafting	
Neurogenic sarcoma	..	..	..	.....	+	..	None	Yes	No evidence of disease 11 yr., 9 mo.
Dermatoleiomyosarcoma	(1) (2)	.. ..	.. ..	7 yr. 10 yr.	+	..	None	No	No evidence of disease 3 yr.
Neurogenic sarcoma	..	..	..	.....	+	..	None	No	No evidence of disease 2 yr., 9 mo.
Sclerosing hemangioma	..	..	..	.....	+	..	1 yr.; wide excision	Yes	No evidence of disease 5 yr., 6 mo.
Dermatofibrosarcoma protuberans	+	..	..	2 wk.	..	+	1 yr. 1 mo.; wide excision	No	No evidence of disease 2 yr., 2 mo.
Leiomyosarcoma	+	..	..	3 wk.	+	..	None	No	No evidence of disease 5 yr., 6 mo.
Sclerosing hemangioma	..	..	..	.....	+	..	3 mo.; excision 1 yr., 4 mo.; excision 10 mo.; excision 9 mo.; excision 8 mo.; excision	No	No evidence of disease 2 mo.
Dermatofibrosarcoma protuberans	..	..	..	.....	+	..	None	No	No evidence of disease 7 mo.
Cancer developing in multiple sebaceous cysts	Twice	..	..	After each operation, last one 2½ yr. ago, 1 yr. later came here	Partial removal of involved scalp			...	Operative death, presumably due to anesthesia

DIAGNOSIS

An analysis of our cases shows that a correct clinical diagnosis of dermatofibrosarcoma protuberans was made in 16 instances (41.0 per cent). In more recent years the correct clinical diagnosis has been consistently made. The next most frequent (and erroneous) diagnoses were neurogenic sarcoma (7 cases) and sclerosing hemangioma (4 cases). Under the microscope and on clinical study the neoplasm has been confused with dermatoleiomyomas originating from the smooth muscles surrounding the hair follicles and apocrine sweat glands. It is histologically similar to the reported picture of dermatofibroma lenticulare or the histiocytoma of Waringer. Dermatofibrosarcoma protuberans may so simulate the clinical appearance of the following lesions as to require a biopsy diagnosis for identification: sclerosing hemangioma, desmoid tumor, fibrosarcoma, neurogenic sarcoma, nonpigmented malignant melanoma, sweat gland carcinoma and wen.

TREATMENT

Radiation Therapy. — Fibrosarcomas in general are not radiosensitive. Irradiation in itself has not been notably successful in the treatment of dermatofibrosarcoma protuberans. McMaster [21] has advocated treatment by wide surgical excision followed routinely by roentgen therapy with the intent to destroy any remaining tumor tissue. We contend this principle to be an improper one, implying as it does the use of an inferior method (irradiation) as a substitute for an incomplete surgical removal. Irradiation as the sole means of therapy has not been used

21. McMaster, P. E.: Sarcomatoid Fibroma of Skin (Progressive and Recurring Dermatofibrosarcoma), Ann. Surg. **99**:338-347, 1934.

for any of our patients treated at the Memorial Hospital. The combined use of surgical excision and irradiation was employed in seven instances. In two of these patients recurrent growths developed 13 months and four years, respectively, after treatment; the recurrent tumors were successfully removed by surgical procedures. Of the remaining five patients, one has been lost for follow-up study and the remaining four have been followed for eight to 19 years, with no evidence of recurrence. Although these results are good, we do not believe that radiation therapy adds any worth while increment to the salvage of these patients. The addition of roentgen ray therapy is not necessary if excision has been complete, and if surgical removal is incomplete, irradiation may delay but will probably not prevent the growth of the residual tumor.

Surgical Treatment.—The treatment of choice is radical surgical excision, and this opinion is shared with the earlier authors (Taylor,[3] Pfeiffer,[12] Kartscher,[11] Coenen,[10] Kuznitsky and Grabisch [7]). Darier [1] and Hoffmann [2] commented on the tendency of the tumor to recur after such procedures as cautery excision and the use of chemical caustics. Johnston in 1903 advocated an excision so wide that a margin of 1 inch (2.54 cm.) of normal tissue would completely surround the lesion. The high rate of recurrence of dermatofibrosarcoma protuberans is due to two factors, namely, failure to appreciate the infiltrative properties of the neoplasm and consequent incomplete removal. Unless the surgeon succeeds in extirpating beyond the fine projecting rami of the tumor and through completely normal tissue, failure follows and recurrence develops. If the tumor is small, one is generally able to excise it adequately and to close the wound primarily without the use of skin grafting. Although suitable incisions, sliding and transposed skin flaps embodying principles of plastic surgery may close the defect, skin grafting is sometimes necessary. We usually have a dermatome immediately available. Simple removal of the lesion with circumferential skin and subcutaneous tissue might prove to be sufficient in many cases, but because of our own experience with recurrences, we now routinely carry the dissection so deeply that the fascia overlying the muscles is removed with the specimen. The subjacent muscles are excised if the dermatofibrosarcoma infiltrates through the fascia. We have never found it necessary to perform an amputation for this tumor. If the abdominal wall is the site of origin, a careful reparative procedure follows excision, in order to prevent the development of a hernia; fascia lata grafts are occasionally helpful. The management of metastases in regional lymph nodes has never been a problem, as we have never observed this complication. Skin grafting has been done in six of the 20 operations for recurrent tumors of this type.

END RESULTS OF TREATMENT

If we were to judge the character of this neoplastic disease solely on the basis of our own experience, we would consider the title of dermatofibrosarcoma to be a misnomer because none of our patients has died of the disease or showed metastases. A proper analysis of the end results of treatment should consider separately patients falling into two categories, namely, those who received their primary or original treatment at the Memorial Hospital (17 cases) and those who received their initial treatment elsewhere and came to us because of recurrent tumors. As well as we know, all except two of the 39 patients are living and well

at this writing, although recurrences developed in eight patients (20.5 per cent) after our surgical treatment, which were successfully controlled by reoperation.

Of the 17 patients who received their primary treatment from us, 14 underwent wide surgical excision and three had combined operative and radiation therapy. Four patients required skin grafts to cover the resultant wound defect. Four patients suffered recurrence of their lesions, of whom three experienced successful reoperations; there was one operative death attributed to anesthesia. One patient has lived 11 years and 9 months since the date of operation.

Of the 22 patients who received their initial treatment elsewhere and came to us with recurrent tumors, 18 had previously undergone local excision only, two had irradiation and two had combined surgical and roentgen ray therapy. The recurrences following local excision developed after intervals of two weeks to 14 years. After irradiation one tumor never completely disappeared and the other one was again evident after a lapse of two years. With the combined operative and radiation treatment, the dermatofibrosarcomas regrew in four months and nine years, respectively. Our disposition of these 21 patients may be adumbrated as follows; one went elsewhere for the operation but has been checked repeatedly by us and is well five and a half years later; four patients received either preoperative or postoperative irradiation, and 16 patients underwent secondary operations. Our four patients in this series in whom recurrences developed were subjected to tertiary excisions by us and had subsequent freedom from evidence of the neoplasm for periods of six months to two years. The longest period of postoperative follow-up observation without recurrence has been 19 years and 7 months.

ENDOMETRIOSIS

Evidence of Tubal Origin in the Distribution of Lesions

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ENDOMETRIOSIS is one of the more serious afflictions of modern woman. Striking in the home-building years from youth [1] to menopause and often causing severe pain, childlessness and dyspareunia as well as intestinal and urinary lesions, the disease affects so many women (probably twice as many as appendicitis [2]) and its treatment is so unsatisfactory [3] that it has become a challenge to modern medicine.

Several theories have been advanced which could explain its development, but there is little evidence that any one of them does, in fact, operate. This report submits evidence, from a study of where endometriosis occurs, to suggest how in some cases it does occur. The evidence is circumstantial and based on the assumption that if material is dropped onto the pelvic peritoneum (implant theory) simple gravity would be one of the agents influencing its distribution. Evidence of gravity influence is presented. No presently suggested mechanism other than implant would be influenced by gravity. However, the evidence of gravity appears in nonconsecutive cases and therefore fails to rule out mechanisms which might have operated in other cases.

METHOD

For several years, Fallon Clinic surgeons have recorded in more than usual detail, by note, sketch or photograph, the locations of individual endometriosal lesions seen at operation. Recently, lesions have been marked immediately after operation on a formal diagram (figs. 1 and 2). The records of some earlier cases were considered precise enough so that the lesions in these also have been mapped. In a total of 430 patients with pelvic endometriosis operated on by these surgeons, data justified the spot mapping of 138 pelves containing lesions small enough to be represented by spots (see "Sources of Error").

From the surgical services of the Fallon Clinic and St. Vincent Hospital.

Read at the annual meeting of the Surgeons' Travel Club, St. Luke's Hospital, Chicago, April 27, 1950.

1. Fallon, J.: Endometriosis in Youth, J. A. M. A. **131**:1405-1406 (Aug. 24) 1946.

2. Fallon, J.; Brosnan, J. T., and Moran, W. G.: Endometriosis: 200 Cases Considered from the Viewpoint of the Practitioner, New England J. Med. **235**:669-673 (Nov. 7) 1946.

3. (*a*) Fallon, J.; Brosnan, J. T.; Manning, J. J.; Moran, W. G.; Meyers, J., and Fletcher, M. E.: Endometriosis: A Report of 400 Cases, Rhode Island M. J. **33**:15-20 (Jan.) 1950. (*b*) Fallon, J.; Brosnan, J. T.; Meyers, J., and Manning, J. J.: The Clinical Aspects of Endometriosis, Ann. West. Med. & Surg. **4**:321-325 (July) 1950.

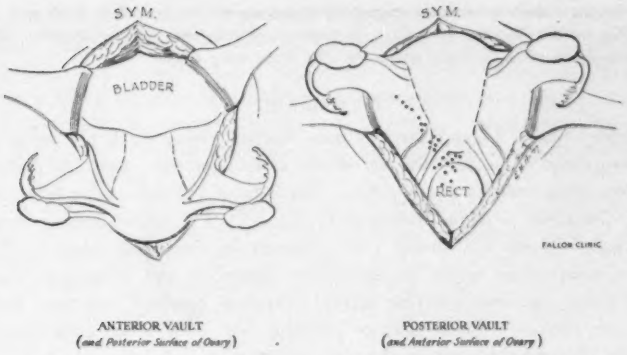

Fig. 1.—The form used for record. Endometriosal lesions less than 1 cm. in diameter are spotted.

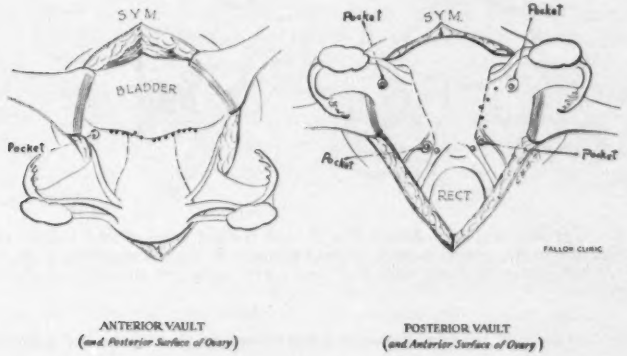

Fig. 2.—A single case illustrating concentration in the uterovesical fold and in anomalous peritoneal pockets.

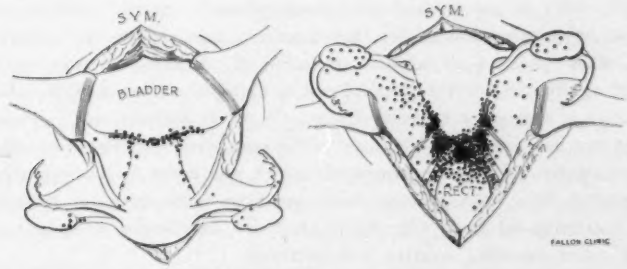

Fig. 3.—Composite spot map of small lesions in 138 cases, showing concentrations in most dependant areas and where uterosacral ligaments and structures around the uterine artery form small peritoneal shelves. This pattern is interpreted as evidence of gravity distribution from a source either in tube or in ovary.

The lesions in each pelvis were spotted on a diagram printed on paper. Each spot map then was traced on the diagram as printed on transparent material (acetate sheet). Finally, the transparencies were stacked and composite spot maps were traced.

FINDINGS

Figure 3 shows a composite spot map of small lesions in all 138 cases. A path of spots extend from near the top of the broad ligament, front and back, to the most dependant portions of the pelvis. The path on the back of the broad ligament also is illustrated in an individual case (fig. 1). The spots increase from above downward. There are strong concentrations in dependant areas. There are lesser concentrations where the uterosacral ligaments and structures in the base of the broad ligament (uterine artery, "cardinal ligament," ureter) raise little peritoneal shelves. These shelves probably are even more prominent in the pelvis in the upright position than at operation.

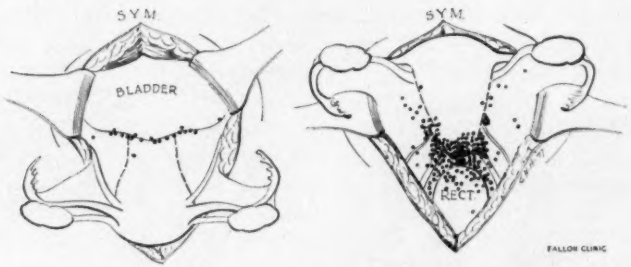

Fig. 4.—Spot map of small lesions in the 69 cases without demonstrated ovarian endometriosis. Persistence of the gravity pattern, without a source in the ovary, points to the tube as a source. (In both composite maps, spots have been moved aside just enough so as not to overlie each other.)

When anomalous peritoneal pockets were present in or near the pathway, they usually contained endometrial tissue (fig. 2).

Of the 138 patients, 64 had proved, probable or possible ovarian endometriosis. (This is an unusually low incidence in the ovary, but because large lesions were excluded, there is an unusual proportion of early cases. Peritoneal lesions, I believe, cause symptoms earlier than ovarian lesions and so are found earlier.) In the other 74 cases all surfaces, including the anterior, of each ovary were searched rigidly; the interior was explored by multiple needle punctures when there was change in tension or increase of size. Of the 74 patients, five had undergone previous ovarian operations. Because of the possibility that these five might have had unrecognized ovarian endometriosis which was cured by the operation, they were omitted from a second composite spot map, made from the transparencies of the remaining 69 cases (fig. 4) to show the distribution of lesions in cases without (demonstrable) ovarian endometriosis.

This second map shows a pattern resembling that of figure 3, although less developed.

INTERPRETATION

Figure 3 (all cases) shows a definite pattern. This pattern is compatible with the distribution of some active agent by gravity. It does not seem compatible with origin from embryonic rests, lymphatic or vascular distribution, metaplasia, heterotopia or extension in continuity from tube or uterus. That the pattern is so clear is a surprise. It was expected to be obscured by variation and disease (see "Sources of Error").

In the anterior vault, the pathway down to the uterovesical reflexion is indicated rather than defined, but the line of spots in the uterovesical reflexion seems unnaturally perfect. Indeed, I would question its validity had I not seen the same string-of-beads phenomenon in several individual cases. One such case was included in the study, contributed many of the spots to this area and is mapped separately in figure 2.

If gravity is a distributing method, then the agent distributed in this pattern should be (*a*) mobile enough to be moved by gravity; (*b*) viscous or adherent enough to be arrested along its course by minor obstacles and (*c*) capable of producing the disease where arrested. One might imagine some viscous chemical capable of stimulating in the cells it touched a hypothetical power of metaplasia, but the only currently known agent which satisfies these conditions is endometrium itself, in fragments or suspension. Therefore the gravity pattern becomes circumstantial evidence for propagation by implantation. Furthermore, if the force distributing an agent over a pathway such as that in figure 3 is gravity, the source of supply should be near the upper end of the path, where the only probable sources are tube and ovary.

Does the path start from the tube, from the ovary or from both? Presumably many of the peritoneal lesions spotted in figure 3 were started by droppings from ovarian endometriomas. But what source supplied the peritoneal lesions in those cases in which there was no visible ovarian edometriosis? The evidence of the gravity pattern persisting in figure 4 points to the tube.

It is possible, of course, that previous endometriosal lesions in the interior of the ovary may have furnished seed for some of these peritoneal lesions and then have shrunk or disappeared without leaving traces on the surface. However, the repetition of this clinically unusual phenomenon through any significant fraction of 69 cases is improbable. It might be added, also, that several patients showed only early lesions, too early to have allowed ovarian lesions time to propagate and then disappear.[4]

It is true, too, that one of the hypotheses offered to explain endometriosis, that of the metamorphosis of ovarian cells into endometrial cells, would locate the source of endometriosis in the apparently normal ovary. Whether such a process could operate without leaving visible residua in the ovary will be unknown until the process itself has been seen. So, until there is more satisfactory evidence of

4. This timing is based on observations made by me during operations at varying periods after presumptive bursts of chocolate cysts in patients and at various intervals between three weeks and five years during a current study of experimental endometriosis in rhesus monkeys. Some lesions considered to be early have been illustrated elsewhere (footnotes 2 and 3*a*).

primary origin in the ovary, the persistence of a gravity pathway pointing to tube or ovary in the 69 cases in which the ovary appeared normal seems to inculpate the tube.

Within the method's limitations, these spot maps therefore constitute circumstantial evidence that in the 138 cases mapped implantation was a method of propagation and the tube a source of implanting material.

SOURCES OF ERROR, LIMITATIONS

In general, spot maps offer only circumstantial evidence. There also are two sources of error peculiar to this application of spot mapping.

In the first place, no map can represent, so fairly as it can the streets of a city, the topography of several pelves with endometriosis or indeed of one normal pelvis from hour to hour as it changes with micturition, defecation and peristalsis. Pelvic variations and diseases were expected to introduce into the final composite map so many exceptions that any pattern it might contain would be hidden. For example, a retroverted uterus, adherent in the cul-de-sac, may so change pelvic topography that the most dependent area is the top of the fundus. However, the expected did not happen, and I do not believe that in this application the factor would operate in the opposite direction to falsify a pattern where none existed, although it may be hiding additional patterns.

Secondly, an endometriosal lesion cannot be mapped so simply as poliomyelitis. Whether the poliomyelitis is mild or fatal, the spot goes to the same place on the map, but an endometriosal lesion may be minute or it may be large enough to involve tube, ovary, broad ligament and uterus. If each of these four areas were allotted a spot, the importance of the lesion would be quadrupled. On the other hand, spotting only the center, or a place where the spotter thought the lesion started, would be subjective. Arbitrarily, therefore, larger lesions were disregarded altogether and only the more exactly localized, small lesions (less than approximately 1 cm. in diameter) were spotted. So far as I could judge, the distribution of large lesions followed that of small ones closely enough so that their inclusion would not have changed the pattern of the maps, but their exclusion does cause two artefacts. Many ovarian lesions are larger than 1 cm. (by the time of operation) and lesions on the middle and upper parts of the posterior surface of the broad ligament tend to be broad adhesions to the ovary. The exclusion of these lesions because of size, therefore, causes a falsely low incidence of spots in the ovaries and on the upper portions of the broad ligaments.

All this is less important than the statistical objection that the material is nonconsecutive. Because of this the maps have no negative value, that is, they rule out no theory or mechanism, because that theory or mechanism might have operated in material which was not mapped.

To what extent does the fact that the cases were nonconsecutive compromise the study's positive value? Although the reason for excluding material was to make the maps as objective as possible, exclusion itself introduces a source of subjective error. Lesions were excluded because they were not exactly localized. Were those which lay outside the pattern in which it was realized lesions were tending to group unconsciously recorded less exactly than those following the

pattern? Not, presumbably, before the existence of a pattern was realized and not, of course, after it was realized that the pattern was worth study. However, there was a brief transition period, while the existence of a pattern was being realized, when some lesions were located unprecisely or not at all. The number of cases in this period was small but cannot now be determined, so that they could be omitted. That the error so introduced is minor is suggested by the fact that the pattern is as clear throughout the first and last thirds of the series as in the middle, which includes the transition. Incidentally, several cases like that shown in figure 1 were recorded early in the series, and the pattern's concentration near the junction of the uterine artery and uterus, which was later recognized to have occurred throughout the early and middle cases, was not realized until maps were transferred to transparencies and stacked.

APPLICATION

John Sampson is remembered, inadequately, as the champion of "wrong way menstruation" in endometriosis. Sampson's great contribution was not imagining a theory but finding a fact, the fact that a diversity of phenomena, being improperly treated under a succession of mistaken diagnoses, constituted one frequent and serious disease. As part of his study he devised, or excavated from libraries, several hypotheses which he assayed by tireless clinical and microscopic observation, but, it must be confessed, with but little experimentation. One cannot grind through all his poorly organized papers without finding much of what since has been said about endometriosis and, incidentally, concluding that their author was not promoting a catch phrase but only seeking truth by weighing possibilities.

Sampson's principal theory was that endometriosis could propagate by implantation.[5] There are cogent arguments to prove that implantation is impossible, but the evidence of this study is that implantation did occur. The evidence suggests that the implants came from the tube. Several explanations have been offered (all by Sampson, and I have none to add) for the discharge of endometriosis-producing material from the tube, such as (1) retrograde menstruation[6]; (2) menstruation by tubal epithelium[7]; (3) intrauterine instrumentation[7]; (4) handling of tubes at operation[7]; (5) spontaneous shedding of tubal epithelium,[7] and (6) shedding from adenomyomas of the tube.[8]

There is no evidence in these spot maps for or against any one of these or other mechanisms operating through the tube; the evidence only points to the tube

5. Sampson, J. A.: Perforating Hemorrhagic (Chocolate) Cysts of the Ovary: Their Importance and Especially Their Relation to Pelvic Adenomas of Endometrial Type ("Adenomyoma" of the Uterus, Rectovaginal Septum, Sigmoid, Etc.), Arch. Surg. **3**:245-323 (Sept.) 1921. (For the historically minded: The paper as printed here contains Sampson's first mention of implantation; a footnote to its printing in Trans. Am. Gynec. Soc. contains his first mention of tubal origin.)

6. Sampson, J. A.: Peritoneal Endometriosis Due to the Menstrual Dissemination of Endometrial Tissue into the Peritoneal Cavity, Am. J. Obst. & Gynec. **14**:422-469 (Oct.) 1927.

7. Sampson, J. A.: Endometriosis Following Salpingectomy, Am. J. Obst. & Gynec. **16**:461-501 (Oct.) 1928.

8. Sampson, J. A.: Pelvic Endometriosis and Tubal Fimbriae, Am. J. Obst. & Gynec. **24**:497-542 (Oct.) 1932.

as a place where some mechanism operated. It is within the province of this paper, nevertheless, to summarize the present status of retrograde menstruation, because important evidence recently has been added to that theory.[9]

All steps of the theory finally have been proved, although step by step rather than collectively. Retrograde menstruation does occur; several surgeons have reported, and I have seen, the occasional presence of menstrual blood in the fimbriated extremity during menstruation. Menstrual blood contains fragments of endometrium. Ectopic fragments of endometrium do produce endometriosis; several investigators have succeeded in implanting excised pieces, and I have produced the condition in monkeys from excised pieces laid on peritoneum rather than implanted in it and also reproduced it by dropping on the surface of the peritoneum the contents of artificial endometriosal cysts. Until recently, however, one important link in the chain of evidence was missing. It had been denied that the endometrial cells in normal menstrual material are viable or, if viable, vigorous enough to implant and grow. Scott and TeLinde[9] now have produced endometriosis in monkeys by somersaulting the uterus so that menstruation was intra-abdominal. That link closes the chain of evidence; retrograde menstruation can cause endometriosis.

Most of what has been written about the etiology of endometriosis, including this paper, deals more with mechanisms than with ultimate causes. For example, if endometriosis comes from retrograde menstruation, why does one woman menstruate retrogressively while another does not? Is retrograde menstruation a universal phenomenon, with some seeds falling on ground which, for unknown reasons, is especially fertile? Why is hematometra from cervical occlusion accompanied with endometriosis in one case and not in another? Why is it difficult, as I have found, to produce tubal backflow in animals by closing the cervix? Is there a mechanical answer in the tubes, or is the observation of Meigs and others[10] that endometriosis tends to occur in women who are not having children a better lead to the fundamental causes and so to the prevention of the disease? The answers to these questions are still unknown.

SUMMARY

Of the theories offered to explain the development of endometriosis,[11] several are reasonable and appear possible but none has been shown actually to operate in patients.

The locations of recorded lesions in 430 patients were studied for intimations of etiology. Records lacking the unusually exact data required for such a study and lesions too large to localize exactly were excluded. These exclusions nullify

9. Scott, R. E., and TeLinde, R. W.: The Production of Experimental Endometriosis in the Rhesus Monkey, presented before the Annual Meeting, American Gynecological Society, White Sulphur Springs, West Virginia, May 11-13, 1950, to be published in Am. J. Obst. & Gynec.

10. Meigs, J. V.: Endometriosis: Its Significance, Ann. Surg. **114**:866-874 (Nov.) 1941. Fallon and others.[2]

11. Ranney, B.: Etiology of Endometriosis, Internat. Abstr. Surg. **86**:313-334 (April) 1948.

all negative value in the study (that is, it cannot rule out any theory of etiology) but, for reasons discussed in detail, it is believed that they do not compromise its positive value.

Spot maps were made of small lesions in 138 cases. A composite spot map of all 138 shows a pattern suggesting gravity distribution and therefore surface implantation. It suggests that the implanting material came from either the tube or the ovary. Persistence of the pattern in a separate map made of those cases in which ovarian lesions were apparently lacking suggests that it came from the tube.

The maps contain no evidence favoring one theory of tubal origin rather than another.

One source of endometriosis is not its cause.

CONCLUSIONS

The maps constitute circumstantial evidence that in the cases mapped some agent which produced endometriosis by implantation proceeded from the tubes and was distributed by gravity.

EFFECT OF ADRENOXYL ON BLOOD LOSS FROM SURGICAL WOUNDS

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AND
K. S. GRIMSON, M.D.
DURHAM, N. C.

IT WAS demonstrated by W. B. Cannon [1] in 1914 that intravenous or subcutaneous injection of small amounts of epinephrine would shorten the coagulation time of blood by one half to two thirds. He also observed that after large doses of epinephrine there was first a lengthening and later a shortening of coagulation time. Stimulation of the splanchnic nerves in animals or the occurrence in man or animals of pain or of emotions such as fear and rage is capable of greatly shortening the coagulation time of blood. After Cannon many observers have demonstrated that epinephrine in large doses causes a rise of blood pressure, increases the rate of circulation and prolongs bleeding immediately after the injection and during the time of increased pressure. The hemostatic action of epinephrine is evident when the hypertension produced by it disappears and this action persists for 15 minutes to six hours. The hemostatic action occurs promptly after doses of epinephrine smaller than those producing appreciable vasoconstriction. There is no direct parallelism between intensity of the sympathicomimetic activity of epinephrine and occurrence of its hemostatic action. Also when an experimental animal is tested after administration of a drug which blocks vasoconstrictor action of epinephrine or after bilateral total sympathectomy,[2] this hemostatic property persists.

The mechanism of the hemostatic action of epinephrine is conventionally explained as follows: Epinephrine (fig. 1 *A*) is completely transformed by oxidation to adrenochrome (fig. 1 *B*), a product possessing marked hemostatic properties. Adrenochrome is hemostatic but is not easily preserved. Despite use of refrigeration or of acid solutions it is soon deposited as a black precipitate of melanin. However, the monosemicarbazone of adrenochrome, adrenoxyl (fig. 1 *C*), is a stable synthetic preparation which produces a hemostatic action like that of epinephrine but does not produce sympathicomimetic effects. This hemostatic action is evident after a latent period of approximately 15 to 30 minutes, the time necessary to convert adrenoxyl to adrenochrome in the tissues of the body.

Aided by a grant from Squibb Institute for Medical Research.

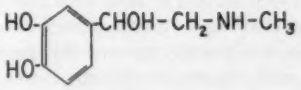
From the Department of Surgery, Duke University School of Medicine.

1. Cannon, W. B., and Mendenhall, W. L.: Factors Affecting the Coagulation Time of Blood: I. The Graphic Method of Recording Coagulation Used in These Experiments, Am. J. Physiol. **34**:225-231, 1914.

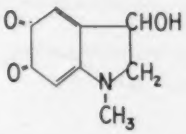
2. Derouaux, G.: Étude du mécanisme de l'action hémostatique de l'adrénaline, Arch. internat. de pharmacodyn. et de thérap. **66**:202-219, 1941.

The effect of adrenoxyl on bleeding time has been studied by many investigators. Roskam, Derouaux, Meys and Swalue [3] demonstrated diminution of the bleeding time in man after intramuscular injection of 100 gamma of adrenoxyl; the greatest effect was a decrease by one third occurring 60 minutes after injection.

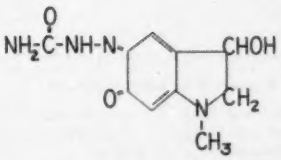
The purpose of our work has been the study of effects of administration of adrenoxyl [4] on bleeding time and also on the amount of bleeding from surgical wounds in rabbits, dogs and man.



(A) EPINEPHRINE



(B) ADRENOCHROME



(C) ADRENOXYL
(Semicarbazone of Adrenochrome)

Fig. 1.—Adrenoxyl is a stable synthetic derivative of adrenochrome, which is an oxidation product of epinephrine.

A. EFFECT OF ADRENOXYL ON BLEEDING TIME

Results of experiments testing the effect of adrenoxyl on the bleeding time of dogs are outlined in figure 2. The method of measurement of bleeding time was that of Roskam and Pauwen.[5] In each dog, as a control, ten bleeding times were

3. Roskam, J.; Derouaux, G.; Meys, L., and Swalue, L.: Un nouvel hémostatique biologique: La mono-semicarbazone d'adrénochrome ou adrénoxyl, Arch. internat. de pharmacodyn. et de thérap. **74**:162-175, 1947.

4. Furnished by the Squibb Institute for Medical Research.

5. Roskam, J., and Pauwen, L.: Une technique et une méthode pour l'étude de l'hémostase spontanée et des médications hémostatiques, Arch. internat. de pharmacodyn. et de thérap. **57**:450-466, 1937.

taken before the administration of adrenoxyl. The average control time for each of five dogs varied from 40 to 78 seconds. Ten gamma of adrenoxyl was then injected intramuscularly. After about 15 minutes five more bleeding times were determined in each dog, and this was repeated at 30, 60 and 90 minutes. Average times of the 10 control tests and of the five readings for each dog at each interval following adrenoxyl are plotted as points on the lines in figure 2. In four dogs bleeding time decreased in 15 minutes and continued downward until the 60 minute interval, after which it again rose. In the fifth dog the trend varied and was lowest at 90 minutes.

A similar study of bleeding time was carried out in four men, two of whom were given 100 gamma of adrenoxyl and two 500 gamma. No significant changes were observed in the pulse rate, respiratory rate, blood pressure, pupillary reactions or clotting time. Averages of the control bleeding times in the two patients given 100 gamma of adrenoxyl were 5 minutes and 50 seconds in one and 6 minutes and 15 seconds in the other. The change after the intramuscular injection in the

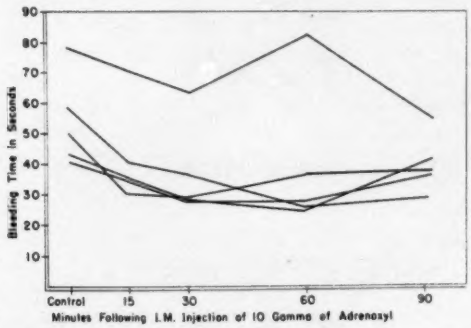


Fig. 2.—Effect of adrenoxyl on bleeding time of dogs. In four of five dogs decrease of bleeding time occurred 15 minutes after administration of adrenoxyl, became more pronounced at 30 and 60 minutes and then less pronounced at 90 minutes.

first was a steady decrease to two minutes by the 75 minute interval and in the second a slow rise to nine minutes and then a fall to four minutes by the 75 minute interval. The two patients given 500 gamma had lower control average bleeding times, 2 minutes and 30 seconds and 2 minutes and 40 seconds, respectively. Averages at consecutive 15 minute intervals fluctuated above and below the control value in the first patient but tended to decrease and reached a low of two minutes by the 90 minute interval. They tended to decrease steadily in the second patient, reaching 50 seconds by the 105 minute interval.

B. EFFECT OF ADRENOXYL ON BLEEDING FROM WOUNDS

The effect of adrenoxyl on blood loss from experimental surgical wounds was studied with the use of several methods. One technic was the making of identical incisions 1 cm. in length on the inferior edge of the right lobe of the liver of anesthetized dogs. The volume of blood lost before the wound stopped bleeding spontaneously was then measured. A second incision was made and blood loss from it was also measured. Ten gamma of adrenoxyl were then administered

intramuscularly and 60 minutes later two more incisions were made attempting to duplicate the first two incisions. This technic was carried out in five dogs. In four the amount of blood lost from the liver one hour after the administration of adrenoxyl decreased markedly when compared with the amount lost before the drug was administered. In the fifth dog spurting arteries were seen in each incision after the drug was given, and the amount of bleeding increased. Results are shown in figure 3.

Another technic was the production of comparable wounds by resecting portions of rabbits' ears. Three incisions were made, each removing a part of the ear. The volume of spontaneous bleeding from each amputation cut was measured. The first wound on the ear was made by resecting a 1 cm. wide section of the tip. The second and third wounds were made by resecting 3 cm. long portions of the ear along the anterior and posterior margins (fig. 4). Immediately after each cut

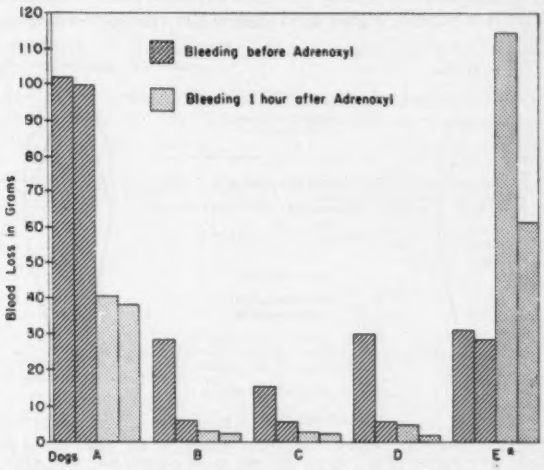


Fig. 3.—Effect of adrenoxyl on blood loss from incisions of the liver. In four of five dogs spontaneous bleeding from two incisions in the liver before administration of adrenoxyl is greater than that from two identical new incisions made an hour after the drug was given. Asterisk indicates occurrence of spurting arteries.

the bleeding edge of the ear was placed in 15 cc. of isotonic sodium chloride for five minutes. The volume of blood and saline solution was measured and the hemoglobin concentration of the solution determined by the Sahli method with a Hellige hemometer. The total number of grams of hemoglobin in the solution was used as the measurement of the amount of bleeding. Five days after the bleeding from one ear had been determined a similar test was made on the other ear. Altogether, 24 rabbits were studied.

The rabbits were divided into three groups of eight animals each. The first group of eight was used as a control, and the amount of bleeding from each ear was determined five days apart without the use of a drug. In the second group the amount of bleeding from one ear was determined without the use of a drug and five days later the amount from the opposite ear was determined one hour after the intramuscular injection of 10 gamma of adrenoxyl. In the third group the

amount of bleeding from the first ear was determined one hour after the administration of 10 gamma of adrenoxyl and five days later the amount from the opposite side was determined without the use of a drug. It is evident (fig. 4) that, with the distal cut only, the loss at the second bleeding in the control group of eight rabbits is considerably less than that at the time of the first bleeding, five days earlier. The bleeding after the administration of adrenoxyl in the eight given the drug before the second bleeding is the same as that in the control. The bleeding from the eight given adrenoxyl before the cuts on the first ear was the least of these groups, though for some unexplained reason the bleeding five days later without any drug was higher in this group. When one considers the average total bleeding from all three cuts on each ear of each group of eight animals (24 cuts) it is evident again that in the control rabbits given no drug the amount of the second bleeding was less. The amount of bleeding in the rabbits given adrenoxyl before the cuts on the second ear was lower than that of the first bleeding in this group but was slightly higher than that of the second bleeding in the controls.

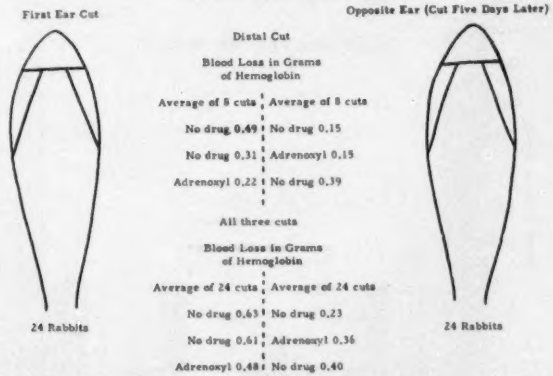


Fig. 4.—Effect of adrenoxyl on bleeding from wounds of the ear. Blood loss in grams of hemoglobin after amputation of the tip of the ear in 24 rabbits and also after two additional lateral cuts is averaged and values presented separately for loss from the distal cut in 8 controls, 8 which received adrenoxyl only before amputation on the second ear and 8 which received adrenoxyl only before amputation of the first ear. Similar average figures are presented for total loss from the three cuts. Operations on the two ears were five days apart.

The group in which adrenoxyl was given before the first cut had the lowest amount of bleeding of the three groups, but, as with the studies of the distal cut alone, the average in this group for the second ear when no drug was used was somewhat higher than that for the second bleeding in the three groups although somewhat less than when adrenoxyl had been used five days earlier.

Other experimental methods to secure identical wounds involving only small vessels and capillaries, such as the removal of split thicknesses of skin with the Paget dermatome and the making of multiple incisions in the skin with the use of an instrument to control depth and length, were unsuccessful because of inability to produce wounds which had comparable amounts of bleeding. The greatest difficulty encountered in all these studies was the occurrence of individual larger arteries which spurted blood.

C. EFFECT OF PREVIOUS BLOOD LOSS ON CONSTITUENTS OF BLOOD

Because of the decrease in blood loss from identical wounds evident five days after the initial bleeding, investigations were carried out on rabbits to determine whether previous bleeding might have significantly altered the constituents of the blood. In five rabbits, 28 to 40 cc. of blood was removed by intracardiac puncture and examined. Five days later an identical procedure was carried out. For convenience, results obtained are tabulated in the accompanying table. It is evident that five days after the first bleeding there was a slight drop in the red blood cell count and a pronounced increase in blood platelets. Bleeding times were determined on these five rabbits before the first and second intracardiac punctures and withdrawal of blood. The bleeding times after five days (table) are lower.

D. EFFECT OF ADRENOXYL ON BLOOD LOSS IN PATIENTS

Blood loss was estimated in patients during operation by weighing the original dry sponges used and weighing the moist sponges as discarded by the operator. Considerable variation of the estimated blood weight occurred from patient to

Changes in Constituents of Blood Following Bleeding in Rabbits

	Before Bleeding				Five Days After Bleeding		
No. of Rabbit	Red Blood Cell Count in Millions	Platelet Count in Millions	Bleeding Time in Seconds	Volume of Blood Drawn, Cc.	Red Blood Cell Count in Millions	Platelet Count in Millions	Bleeding Time in Seconds
1.....	2.48	0.496	82	45	2.1	1.00	180 *
2.....	3.6	0.360	90	28	3.5	1.20	49
3.....	3.7	0.550	91	30	3.4	1.00	57
4.....	2.55	0.255	67	30	2.3	0.920	26
5.....	3.79	0.379	63	30	2.7	0.700	45
Average.....	3.21	0.401	79	33	2.8	0.96	44

Note: Determinations of body weight, hemoglobin, hematocrit, clotting time and prothrombin time did not reveal significant changes.
* Aberrant value of 180 omitted from average.

patient and from operator to operator. Technics varied, and the number of large bleeding arteries encountered was not constant. An attempt was made to determine blood loss during removal of tonsils and adenoids in nine patients not receiving adrenoxyl. Estimated weights of blood, saliva and mucus lost during tonsillectomy and the removal of adenoids averaged 294.3 Gm. but varied widely, the range being from 125.4 to 423.9 Gm. Inguinal herniorrhaphy and radical mastectomy were then selected as operations for study, measuring blood loss in a consecutive series of operations but treating only alternate patients. The treated patients received 100 gamma of adrenoxyl one hour before operation and subsequently 100 gamma every half hour until the end of the operation. Of 11 patients who underwent radical mastectomy for carcinoma of the breast, 5 were alternate untreated patients, and blood loss averaged 531.3 Gm., with a range from 455.3 to 627.2. Six were treated with adrenoxyl, and their average loss was 737.3 Gm., with a range from 299.8 to 1,296.7. The largest figure, 1,296.7, and two other high figures, 1,057.5 and 997.4, which raised this average occurred in obese patients requiring extensive plastic procedures to close the wounds. Further studies were not undertaken because of the obvious variations in the size of breasts removed and in the extent of the operation employed.

Studies were made of alternate patients treated with adrenoxyl in a series of 16 undergoing inguinal herniorrhaphy. The blood loss in nine controls averaged 51.9 Gm. and ranged from 12.9 to 121.3 Gm. The seven patients treated with adrenoxyl had a blood loss averaging 53.5 Gm., with a range from 32.1 to 83.9. Because of the great number of variables connected with this study using small amounts of adrenoxyl (100 gamma injections), no definite conclusions can be drawn.

SUMMARY

The effect of adrenoxyl on the bleeding time of dogs was studied. In five dogs normal bleeding times were determined and were 15, 30, 60 and 90 minutes after the administration of 10 gamma of adrenoxyl. There was a marked decrease in the bleeding time. The maximum effect was noted at 30 and 60 minutes. By 90 minutes the effect began to wear off and the bleeding time again increased. Similar results were obtained in patients after the administration of 100 and 500 gamma of adrenoxyl.

Surgical wounds were produced in animals, and the effect of adrenoxyl on bleeding from these wounds was studied. Incisions were made into the edge of the livers of dogs, and in four the bleeding one hour after the intramuscular administration of 10 gamma of adrenoxyl decreased by an average of 74.5 per cent. In the fifth, two small spurting vessels were severed, and it was apparent that these incisions were not comparable to the control incisions.

Portions of a rabbit's ear were resected, and the amount of bleeding with and without the intramuscular administration of 10 gamma of adrenoxyl was measured in the same animal after five days. Two factors were found to decrease the amount of bleeding. In addition to the effect of adrenoxyl, bleeding the animal five days after it was bled before produced a separate effect, apparently by definitely increasing the number of platelets and slightly decreasing the number of red blood cells. Bleeding from wounds made during surgical intervention in patients was found to be variable, and the possible value of the use of adrenoxyl as a method of reducing bleeding during operations could not be determined by the methods employed and the small amount of the drug used.

CONCLUSIONS

Adrenoxyl produced a notable decrease in the bleeding time of dog and man. There was a latent period of 30 to 60 minutes before the maximum effect appeared. It was difficult to produce identical surgical wounds in which the effect of adrenoxyl could be studied. Bleeding from the donor sites of skin grafts and from multiple skin incisions in dogs was too variable to be used. Bleeding during standard operations on patients was also too variable to permit valid study.

In small wounds of the liver of dogs in which no spurting bleeding arteries were encountered, adrenoxyl decreased the amount of blood loss an average of 75 per cent. Adrenoxyl decreased the amount of bleeding after resection of a portion of a rabbit's ear. The effect was greatest on wounds in which small arterioles, venules or capillaries were severed and in which there was a slow, steady ooze rather than vigorous bleeding. From these observations it appears that adrenoxyl might have a clinical use in decreasing the amount of blood loss

from surgical wounds, especially if the surgeon maintains careful control of larger visible arteries spurting blood. However, we have not yet obtained clinical evidence to support this assumption or devised a suitable method to test it. The drug is evidently well tolerated by patients. As yet, untoward side effects have not been encountered.

Regularly, the amount of bleeding from a second wound in rabbits made five days after the first was less than that from the orignal incision.

CAUSE AND TREATMENT OF PRURITUS ANI

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THE SUCCESSFUL treatment of pruritus ani depends on understanding its cause. In 1936 Hellwig and I [1] presented the results of our histological study of 43 cases of pruritus and concluded that this disease is the manifestation of a chemical dermatitis. Since then, almost 100 papers have appeared in the literature, and there is still much controversy concerning the cause of this distressing condition.

ETIOLOGICAL FACTORS

The etiological factors which, during the last decade, have been regarded as responsible for pruritus ani can be divided into five groups:

1. Nervous disorders often underlie pruritus, according to Drueck (1943),[2] and may range from simple instability to true psychosis. Bacon and Smith (1949) [3] believe that a disturbance in the sympathetic nervous system may reduce the threshold to the sensation of itching. In five patients with intractable pruritus that had not responded to therapy, these authors obtained immediate relief by a short series of procaine blocks of the sympathetic ganglions. Bodkin (1945),[4] finding no cause except a pronounced emotional disturbance, obtained prompt relief of itching in 42 patients by giving diphenylhydantoin (dilantin®) sodium and powdered vegetable diastase (taka-diastase®). In the newest edition of "Diseases of the Skin" by Ormsby and Montgomery,[5] pruritus ani is discussed in the chapter on neuroses.

2. Endocrine disorders, such as thyroid disease, hypopituitarism, diabetes and hypoadrenia, were mentioned by Postlethwaite (1936) [6] as predisposing factors, while ovarian disturbances have been cited by Neilsen (1941),[7] Turunen (1940) [8] and Wilson (1943).[9]

Read before the Section on Gastro-Enterology and Proctology at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 29, 1950.

1. Tucker, C. C., and Hellwig, C. A.: Pruritus Ani: Histologic Picture in Forty-Three Cases, Arch. Surg. **34**:929 (May) 1937.

2. Drueck, C. J.: Essential Pruritus Perinei, J. Nerv. & Ment. Dis. **97**:528, 1943.

3. Bacon, H. E., and Smith, C. H., cited by Bacon, H. E.: Anus, Rectum, Sigmoid Colon: Diagnosis and Treatment, ed. 3, Philadelphia, J. B. Lippincott Company, 1949, vol. 1, p. 228.

4. Bodkin, L. G.: Oral Therapy for Pruritus Ani, Am. J. Digest. Dis. **12**:255, 1945.

5. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1948, p. 1069.

6. Postlethwaite, F. M., cited by Bacon, H. E.: Anus, Rectum, Sigmoid Colon: Diagnosis and Treatment, ed. 3, Philadelphia, J. B. Lippincott Company, 1949, vol. 1, p. 225.

7. Neilsen, N.: Hormone Treatment of Pruritus Ani, Nord. med. **9**:850, 1941.

8. Turunen, A.: Follicular Hormone in Therapy of Pruritus During Pregnancy, Duodecim **56**:348, 1940.

9. Wilson, C. C.: Pruritus Ani Associated with Menstruation, J. Missouri M. A. **40**:312, 1943.

3. Over the last 14 years allergy has been suggested as an etiological factor. Individual sensitivity, probably on a hereditary basis (Hailey and Hailey, 1939),[10] is regarded by many proctologists as the principal cause of pruritic syndrome. Andresen (1939),[11] Martin (1940),[12] Brooke (1939),[13] Schwartz (1940),[14] Spiller (1937) [15] and Sulzberger (1936) [16] regard pruritus as an allergic reaction to such agents as food, infection and drugs. An abnormality in the production of histamine has been suggested as a cause of pruritus by McCutchan (1945) [17] and Parrot (1943).[18] Vitamin deficiency, both A and B, has been cited by Gabriel (1945) [19] and Spies (1940).[20]

4. Mycotic infection is the responsible factor in pruritus ani, according to Caskey (1939),[21] Terrell (1940) [22] and Seletz (1942).[23] A careful survey of 301 cases of pruritus by Hill (1940) [24] revealed primary or distant fungous infection in 65 per cent. In 60 per cent of the positive cases, Hill found a coexisting dermatophytosis of the feet, and in a few cases an allied seborrheic eczema was also present. He concluded that pruritus ani is the result of a primary invasion by a dermatophyte of the perianal skin or of a dermatophytid reaction of the perianal tissue to a distant focus of fungous infection, most frequently localized on the feet. In the discussion on Hill's paper, Thiele (1940),[25] Allen [26] and Lescale [27] accepted the view that the large majority of cases of pruritus ani are due to infection with ringworm.

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10. Hailey, H., and Hailey, H.: Pruritus Ani et Vulvae, Arch. Dermat. & Syph. **40**:726 (Nov.) 1939.

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13. Brooke, B. R.: Perineal Pruritus, an Allergic Manifestation? Northwest Med. **38**:462, 1939.

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17. McCutchan, G. R.: Pruritus Ani, Am. J. Digest. Dis. **12**:171, 1945.

18. Parrot, J. L.: Sur le mécanisme périphérique de la douleur: Intervention de l'histamine dans la brûlure et le prurit, Compt. rend. Soc. de biol. **137**:620, 1943.

19. Gabriel, W. B.: The Principles and Practice of Rectal Surgery, ed. 3, London, H. K. Lewis & Co., Ltd., 1945, p. 204.

20. Spies, T. D.; Hightower, D. P., and Hubbard, L. H.: Some Recent Advances in Vitamin Therapy, J. A. M. A. **115**:292 (July 27) 1940.

21. Caskey, C. R.: Pruritus Ani, California & West. Med. **50**:14, 1939.

22. Terrell, E. H., in discussion on Hill, M. R.: Etiologic Relationship Between Dermatophytosis and Pruritus Ani, Tr. Am. Proct. Soc. **41**:217, 1940.

23. Seletz, R.: Pruritus Ani and Vulvae; Diagnosis and Management, West. J. Surg. **50**:289, 1942.

24. Hill, M. R.: Etiologic Relationship Between Dermatophytosis and Pruritus Ani, Tr. Am. Proct. Soc. **41**:210, 1940.

25. Thiele, G. H., in discussion on Hill.[24]

26. Allen, J. H., in discussion on Hill.[24]

27. Lescale, M., in discussion on Hill.[24]

5. Chemical factors, i. e., irritating chemical compounds present in feces and brought in contact with the perianal skin, may cause pruritus. The histological alterations of the skin in pruritus ani, which we described in 1936, resemble closely those produced experimentally by the injection of skatole into the skin of rabbits (Stoeber and Wacker, 1940),[28] and we concluded that pruritus ani could be best explained as a chemical dermatitis due to contact with putrefactive products of meat proteins. Hoelzel (1947),[29] as well as Friedman, Haskell and Snape (1948),[30] believes that leakage of material from the anal orifice is responsible for the skin irritation and itching, since the drainage material has proteolytic properties similar to those of trypsin.

Supporting the contention of irritating meat products in feces as an etiological factor is the experience of Buie,[31] who described a 33 year old man with intractable pruritus in spite of hemorrhoidectomy, nerve sections, roentgen therapy and various local injections. Observing dramatic exacerbations apparently related to diet, Buie relieved the patient completely of itching by placing him on a meat-free regimen. Also, I personally was told by an Indian physician that he had seen no pruritus in his Hindu patients who were strict vegetarians.

According to Granet (1940),[32] a chemical dermatitis due to decomposition products of meat proteins best explains the clinical experience that most patients with mild pruritus ani will become symptom free with strict perianal hygiene. Toilet tissue used after defecation actually rubs the irritating fecal substances into the perianal skin. Most proctologists who treat pruritus agree that absorbent cotton should replace the toilet paper.

Granet [32] believes as I do that these irritating substances are end products of bacterial action on meat proteins (indole, phenol, skatole). He was able to produce chemical dermatitis in certain persons by applying solutions of indole and skatole as a patch test.

Of great interest are the results of his treatment of 100 patients with severe pruritus after removing associated anal lesions surgically. His method was then maintenance of perianal cleanliness only. Rectal enemas followed defecation. Cotton and dusting powder were used for cleaning perianal skin four times daily, and no toilet paper was permitted.

Follow-up observations after six to 12 months in 80 patients showed 93 per cent claiming good to excellent results. The best results were obtained in the most cooperative patients, regardless of the amount of skin change or the duration of the disease. After six more months 50 patients were reexamined, and of these 80 per cent reported recurrence of pruritus on cessation of treatment. Only 10 patients remained free of symptoms.

It is my belief that a strict avoidance of meat in the diet and utmost perianal hygiene, on Granet's principles, will cure the majority of cases of essential pruritus.

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28. Stoeber, H., and Wacker, L.: Ein weiterer Beitrag zur Erzeugung atypischer Epithelwucherungen mit Eiweissfäulnissprodukten, München. med. Wchnschr. **57**:947, 1910.

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31. Buie, L. A.: Practical Proctology, Philadelphia, W. B. Saunders Company, 1937, p. 228.

32. Granet, E.: Pruritus Ani: Etiologic Factors and Treatment in 100 Cases, New England J. Med. **223**:1015, 1940.

I doubt that fungous infection is the primary cause of anal pruritus, although fungi may play a certain role as secondary invaders. The histological changes of early stages of pruritus certainly do not favor a mycotic origin.

HISTOLOGICAL STAGES

In Buie's book "Practical Proctology" (1937), Montgomery [33] groups the histological changes of pruritus ani into three stages, depending on duration and severity of the process. In the first stage, little or no thickening of the perianal skin is noticed clinically, although definite histological changes are present. This stage is recognized by intercellular and intracellular edema in the prickle cell layer, dilatation of the superficial blood and lymph vessels and mild perivascular infiltration. There is definite acanthosis. In his second stage, Montgomery describes both clinical and microscopic evidence of thickening of the epidermis. The rete ridges become broad, as well as elongated. Notable hyperkeratotic plugging of the hair follicles occurs, associated with irregular proliferation of the wall of the hair follicles. As the condition becomes more advanced, tremendous thickening of the walls of the hair follicles is seen. The sebaceous glands usually are completely lacking. In the late stages ulceration may be encountered. In the main, our own studies correspond with and substantiate Montgomery's findings, except that in the third stage we observed marked atrophy of the epidermis in addition to the atrophy of the sebaceous glands. In 1936 we distinguished the following four stages of pruritus, based on the histopathological findings in 43 cases:

1. Swelling of the prickle cell layer due to intracellular and intercellular edema. Dilatation of blood and lymph vessels and perivascular round cell infiltration of the corium.

2. Pronounced proliferation of the epidermis, with elongation and thickening of the rete pegs. Hyperkeratosis and plugging of hair follicles.

3. Atrophy of the epidermis and especially of the hair follicles and sebaceous glands.

4. Multiple epithelial defects with excoriations, deep fissures and shallow ulcers.

From the routine microscopic study of pruritic lesions during the last 12 years, I feel justified in adhering to our classification of four stages, and I believe that the histological grading of the lesions not only has academic interest but has a definite practical value in regard to prognosis and treatment.

Among 400 persons with pruritus operated on since 1937, I found changes of grade 1 in 152 patients (38 per cent), of grade 2 in 224 patients (56 per cent), of grade 3 in 16 patients (4 per cent) and of grade 4 in eight (2 per cent).

METHOD OF TREATMENT

The multiplicity of medical remedies for pruritus ani demonstrates the incomplete adequacy of any one. However, I have found of value the exclusion of highly seasoned food and all meats except white meat of chicken and fresh fish. Few drugs have any beneficial effects. Sticky ointments are to be avoided, for it is quite important to keep the part dry in all stages of pruritus. I use only one drug, 2 per cent aqueous solution of brilliant green, which is applied to the itching

33. Montgomery, H.: Histopathology of Anal Pruritus, in Buie,[31] p. 231.

parts after the anus is thoroughly cleansed with soap and water and dried; then compound benzoin tincture is applied. This should be done daily for several weeks.

Further, after each stool the patient is instructed to cleanse the anus using soap and water with hospital cotton, dry the parts, sponge with alcohol, then dust with corn starch. This can be done several times a day when the outside skin is moist, as the majority of pruritus victims have relaxed anal sphincters and there is some bowel secretion.

The vast majority of persons with pruritus ani require surgical treatment regardless of the histological stage of the disease. The second stage is by far the commonest seen on surgical intervention, but more than one stage will be represented in one case.

Fourth stage lesions are somewhat rare and are the most difficult to treat. In first stage lesions one undercutting operation is sufficient for cure. With changes of the second stage, occasionally a second operation is necessary, and pruritus of the third and fourth stages requires a second and even a third undercutting procedure in about half the cases before the skin returns to normal. But after all other rectal lesions have been removed, succeeding operations are not severe.

PREOPERATIVE PREPARATION

The preoperative routine is to give 3 grains (0.19 Gm.) of vinbarbital (delvinal®) sodium the night before the surgical procedure. This is followed the next morning with 1 grain (0.06 Gm.) of vinbarbital sodium one hour before operation and ⅓ grain (0.02 Gm.) of pantopon® (a mixture of the hydrochlorides of the opium alkaloids) one-half hour before the operation. Local anesthesia is induced, employing 0.5 per cent procaine (novocain®) hydrochloride with 5 drops of epinephrine to each ounce (30 cc.).

The patient is placed in the left Sims position, with the knees flexed on the abdomen. After having been prepared by scrubbing with soap and water, the perineum is washed with ether and painted with tincture mercocresols (mercresin®). All the structures about the anus to a level well above the internal sphincter should be infiltrated. This requires from 6 to 12 ounces (180 to 360 cc.) of 0.5 per cent procaine solution. The nerve supply of the external sphincter is derived from the third and fourth sacral and superficial branches of the internal pudic and the lesser sphincterial nerves. I prefer using two 10 cc. B & D three finger Luer-Lok syringes. Three inch (7.6 cm.) 22 gage needles are used, and all needles should be flexible.

I begin the production of local anesthesia by making a wheal 1 inch (2.5 cm.) posterior to the anal orifice with a fine needle. I then insert a 3 inch needle in the wheal and infiltrate laterally each side of the posterior half of the anus, dealing with the anterior half in the same way. Then with one finger inserted in the rectum, I inject the solution close up to the rectal wall for a depth of 2 inches (5 cm.) in the right and left posterior quadrants. The right and left anterior quadrants are dealt with in like manner. One can feel the flow of the solution along the finger, and there should be a steady flow of solution ahead of the needle. Care should be taken not to distort the operative field, and one should allow an elapse of five minutes before beginning dilation, which should be done in the following manner:

The index finger of each hand is inserted in the anterior and posterior commissures, and by slow and continuous traction the muscle gradually relaxes, but should a pecten band be found it should be divided.

TECHNIC OF SURGICAL OPERATION

With a scalpel, make the incision in the midline 1 inch from the posterior commissure just underneath the skin and carry it around the anus to the anterior commissure. Bring the scalpel through the skin at a point in midline about 1 inch from the anus, severing all the nerves to and beyond the pruritic area.

Insert one finger in the anal canal as a guide. When the nerves are severed up to the anorectal line, the knife should be kept forward to prevent injury to the sphincter muscles.

Both sides are treated alike. If in a man there is itching up to the scrotum, the nerves should be undercut in that region. If in a woman there is itching of the

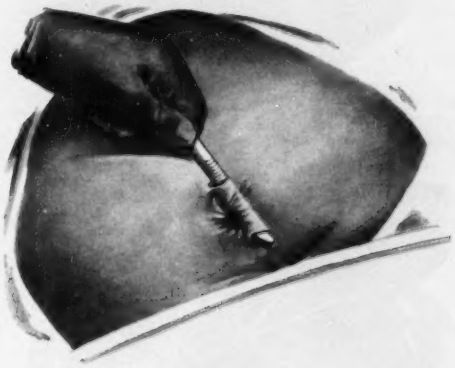

Fig. 1.—Knife is inserted 1 inch (2.5 cm.) from the posterior commissure, and the point of the knife brought out 1 inch anterior to the anus.

labia, the nerves should be undercut, but if the pubes are involved, I inject 1 : 5,000 hydrochloric acid solution under the skin, using as much as 6 ounces around the pubes after the tissues have been infiltrated with procaine hydrochloride. Occasionally, there is an extensive slough.

If there is itching in the sacral region, the nerves are also undercut. A pair of curved scissors should be inserted in the posterior incision and the bridges of tissue separated; the same is done in the anterior commissure. A Penrose drain is split and inserted in the posterior opening and carried out through the anterior opening on each side. Place a pair of Pennington triangular forceps on the skin at the anterior and posterior commissures with the points on the skin midway between the anterior and the posterior commissures. By a slight traction on these forceps, the anal canal can be everted exposing the rectal lesions, such conditions as internal hemorrhoids, infected anal ducts, crypts and enlarged papillae, which usually accompany pruritus. The hemmorrhoids may number three to seven and are dealt with in the following manner. A six inch (15 cm.) curved forceps is placed on the

hemorrhoids. The right anterior hemorrhoid extends farther up the rectum, has no coexisting growths and needs to be seized by a pair of forceps by itself. The right posterior hemorrhoid is now dealt with, along with two secondary growths which may have developed with this one and can be included with one grasp of the forceps. Finally, the left hemorrhoid is taken, with any secondary growths. Even when as many as seven hemorrhoids have developed they can be grouped under three excisions.

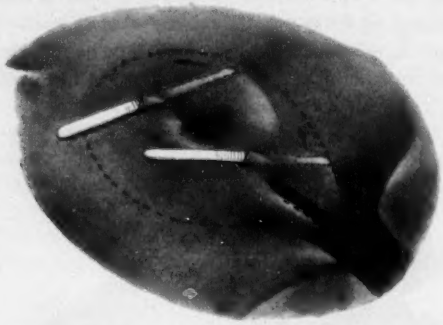

Fig. 2.—Nerves are severed up to the anorectal line and subcutaneously around the anus.

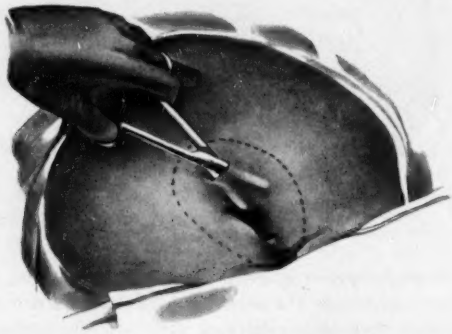

Fig. 3.—Pair of curved scissors is inserted in posterior incision and bridges of tissue are separated. Same process is carried out in anterior commissure.

As a fourth step, grasp the forceps of the right anterior hemorrhoid with the left hand, with the index finger over the growth, making slight traction and at the same time elevating the pile. The hemorrhoid is dissected upward until it is attached by a narrow pedicle which contains the main blood supply.

In the fifth step, either a strong linen (I use a special buttonhole shoe linen) or a heavy braided silk ligature is applied about the pedicle as high up as possible while an assistant makes gentle traction. The ligature should be drawn tightly with a knot on the bowel aspect. Cut squarely across the pedicle; enough stump should be left that there is no danger of its slipping through the ligature and causing hemorrhage. The right posterior and left hemorrhoids are dealt with in the same

way. If too much tissue is included in the ligature, the tissue can be split and two ligatures applied, carrying one just a little higher than the other.

In the sixth step, the tissue containing the ducts, crypt and enlarged papilla is grasped with curved hemostats and dissected out down to the external sphincter muscle, which is exposed. All ducts, crypts and papillae should be removed. The skin tags are excised giving drainage to the hemorrhoid and ducts.

As a final step, pass a speculum into the rectum and by gentle divulsion overcome any narrowing and also see that there is no bleeding inside the rectum. If bleeding, the edges can be approximated by plain 0 interrupted sutures, but in cases of pruritus ani I prefer not to use any sutures, so as to give free drainage. I insert Gaston's rectal glue immediately after operation, and gauze dressings are applied to the outer surface. The glue is inserted into the rectum three times a day. The external parts are cleansed several times a day. Hot packs are applied and changed every two hours. Opiates are given if necessary.

Follow-Up Reports on One Hundred of the Four Hundred Patients Operated on for Pruritus Ani

No. questionnaires sent out..... 100
No. returned because of improper address..... 10
No. returned with answer..... 80

		Stages of Pruritus Ani [1]					
	No. Patients	First	Second	Third	Second and Third	Fourth	Results
No itching.....	60	13	35	3	9	..	75% cured
Slight itching.....	12	2	10	..	..	..	15% slight itching
Severe itching.....	8	..	2	2	..	4	10% severe itching

CONCLUSIONS

The undercutting operation with complete removal of rectal lesions gives good results in a vast majority of cases. But, as stated, some refractory cases of the second stage require a second undercutting operation. Lesions of the third and fourth stages require from two to three undercutting operations in about 50 per cent of cases before the skin returns to its normal state. The parts should be cleansed with soap and water at least once daily until the skin has returned to its normal condition. Meat should be excluded from the diet over a long period, with gradual resumption after the surgical procedure.

ABSTRACT OF DISCUSSION

DR. ALBERT H. ROWE, Oakland, Calif.: Allergic causes of pruritus ani only will be discussed.

Contact allergy must be adequately investigated. Clothing, toilet articles, locally applied drugs and other contactants must be suspected. Relief from their elimination indicates the cause.

Atopic allergy due to blood-borne allergens may be more important. As in atopic dermatitis, its causes—food, inhalant, drug (by ingestion or parenterally) or infectant allergen—must be considered. Food allergy is suggested by its other allergic manifestations, by food dislikes or disagreements, by exaggeration of pruritus in the fall to spring months and, at times, by definite positive scratch test reactions. However, most chronic food allergy is not indicated by positive reactions.

Food allergy may be relieved by exclusion of foods suspected through dietary history or skin testing. Usually diet trial is required. For this I have long used my standardized elimination diets. Good results require strict dieting for adequate periods, as I have advised.

Inhalant allergy must be suspected when pruritus is exaggerated in the pollen seasons or with inhalation of house dust, animal emanations or other inhalants. Skin testing with important inhalants is necessary. Reactions, especially to the scratch test, may be negative. Exaggeration of dermatitis by skin testing occurs. Treatment requires desensitization to those inhalants that cannot be eliminated from the patient's inspired air. As in allergic dermatitis I find that dilutions in the millions or billions often are required, especially during the pollen seasons, to relieve pruritus. Skin and clinical titrations beginning with such weak dilutions that no conceivable exaggeration of the pruritus can result determine the initial doses. With improvement doses of stronger dilution are injected as tolerated. Some cases are controlled with dilutions no higher than 1:50,000,000,000 or weaker during the first year. Inhalant allergy may also require environmental control and a pollen and dust filter.

That ingested and injected drugs may produce this atopic pruritus with or without other involvement of skin areas must be remembered. Occasionally pruritus ani due to allergens from foci of infection or other infectants occurs. Other manifestations of atopic allergy may be absent.

DR. MALCOLM R. HILL, Los Angeles: Pruritus ani is a disease entity involving the integumental areas around the anus and of the perineum, which is inclined to become intractable in nature.

The author's presentation is one which covers the field in a very acceptable manner. He has emphasized the need of removing all anal lesions to achieve the desired result. Mention has been made of the need of perianal hygiene. The surgical approach outlined in the treatment of pruritus is one of merit. I have personally had occasion to see the author at work in the surgical amphitheater, and I fully believe he is a skilled operator in this field.

DR. A. F. R. ANDRESEN, Brooklyn: I am in complete agreement with everything Dr. Rowe has said. I have had experience with everything he has done, and I know that if we consider allergy as the cause of pruritus ani it will practically never be necessary to subject patients to the drastic operations which have been suggested. I long ago realized that pruritus ani, except in cases in which it was due to actual organic disease, such as hemorrhoids or rectal neoplasms, is practically always due to allergy. The allergic reaction is not necessarily an allergic dermatitis, but a similar mucosal reaction may be present in the form of an allergic papillitis, cryptitis or proctitis with ulceration, the so-called fissures in ano. I have seen all these conditions clear up with dietetic treatment alone after discovery and withdrawal of allergic factors. It is really too bad that so few clinicians care to spend the time and energy required for a careful diet study for allergy. Any competent physician, be he specialist or general practitioner, can get the same results that Dr. Rowe describes if he will give the time to the study of his patients.

DR. CLAUDE C. TUCKER, Wichita, Kan.: Dr. Rowe has stated that allergy is the cause of hemorrhoids and pruritus ani. I disagree, for hemorrhoids are caused by infection originating in the anal ducts and leading to a chronic infection in the surrounding tissue. Hemorrhoids and anal ducts harbor skatole which bathes the outerside skin and gets under the skin folds, thus setting up a dermatitis. Therefore, it is quite important to remove all the rectal lesions, as well as to undercut the nerves.

VOLVULUS OF THE SIGMOID COLON

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VOLVULUS is defined by Laurell [1] as a torsion of the bowel on its mesentery which produces symptoms due to narrowing, strangulation or both. The geographic incidence of volvulus varies. In middle Europe, Scandinavia, Russia and India it is a rather common cause of intestinal obstruction, whereas in western Europe, the United Kingdom and North America it is encountered infrequently. According to Wangensteen,[2] about 10 per cent of all intestinal obstructions in this country are secondary to volvulus. Since the sigmoid is involved in not more than 20 per cent of these, volvulus of the sigmoid, then, should account for not more than 2 per cent of all intestinal obstructions. Statistical data from the more recent American literature tend to confirm this figure of 2 per cent.

THE PRESENT STUDY: MATERIALS AND METHODS

This study comprised an analysis of the records of 16 patients who had volvulus of the sigmoid colon and were treated at the Mayo Clinic during the 39 year period Jan. 1, 1908, through Dec. 31, 1946. Only cases in which volvulus represented the sole cause of obstruction were included. Volvulus complicating neoplasm or diverticulitis, for example, was excluded. In each instance the phenomenon was verified either at the operating table or in the postmortem room. Gross and microscopic studies of all surgical or necropsy specimens were undertaken. Follow-up information was obtained on all but 2 cases.

ANALYSIS OF CASES AND COMMENT

It has been stated that volvulus occurs more frequently in the sigmoid colon than in other portions of the intestinal tract. Actually, in this country volvulus of the sigmoid probably accounts for not more than 20 per cent of all intestinal

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Abridgment of thesis submitted by Dr. Hilton to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

1. Laurell, H.: Some Cases of Volvulus, Acta. radiol. **3**:213-214, 1924; Volvulus der Flexura sigmoidea: Eine klinische-röntgenologische Studie, Acta radiol. **7**:105-141, 1926.

2. Wangensteen, O. H.: Volvulus, in Wangensteen, O. H.: Intestinal Obstructions: A Physiological and Clinical Consideration with Emphasis on Therapy; Including Description of Operative Procedures, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1945, chap. 10, pp. 383-395.

torsions. The distribution of volvulus throughout the intestinal tract in this series corresponds closely with the findings of Sweet.[3] In his group of 50 cases of volvulus the small intestine was involved in 69 per cent, the sigmoid in 19 per cent and the cecum in 12 per cent. In our series the small intestine accounted for 73 per cent, the sigmoid for 18 per cent and the cecum for 9 per cent of the cases.

The acute form of volvulus in this series was characterized by a rapid progression of symptoms, with distention and obstipation predominating. Pain, which was usually cramping and generalized, was ordinarily severe. Inquiry into the past history revealed previous obstructive episodes in two thirds and long-standing constipation in one third of the cases. Obstruction was complete in every case, and the incidence of infarction was 66 per cent. Thirty-seven per cent of the series belonged in this category, and the older age groups were affected chiefly.

The subacute form was characterized by a more gradual and irregular progression of symptoms, with development, as a rule, of lesser degrees of distention. Pain was generally less severe and tended to localize in the lower quadrants, especially the left lower quadrant. Four fifths of the patients had experienced previous obstructive episodes, and one half gave a history of long-standing constipation. Obstruction was incomplete in every case, and there was no instance of infarction of the bowel. Sixty-three per cent of the patients belonged in this category of incomplete obstruction, representing principally a younger age group.

The administration of tap water enemas as a diagnostic aid was not undertaken in any case in this series. Roentgenologic data gave, on the whole, little information. In two patients with acute manifestations scout roentgenograms revealed enormous distention of the sigmoid loop, and this was considered pathognomonic of volvulus. In one patient, also with acute symptoms, a roentgenogram made with the aid of a barium enema revealed the typical "bird's bill" or "ace of spades" deformity of the proximal part of the rectum. In the subacute group, neither barium enemas nor scout roentgenograms rendered much help in assessing the underlying disorder.

Detorsion with or without complementary procedures contrived to prevent recurrence was carried out in six patients. Obstruction was incomplete and the bowel was, of course, viable in all. In several, it was the procedure of election because long-standing poor health had rendered the patients poor risks for resection. The immediate postoperative mortality, which for patients in this category was zero, would seem to commend this method of handling volvulus of the sigmoid. The recurrence rate following simple detorsion, however, renders it a "second best" procedure except possibly in poor risk patients. Recurrence rates following conservative surgical treatment reported in the literature have been in the neighborhood of 20 per cent or more, and a recurrence may ultimately mean a fatality. Among the five patients followed up, there has been a recurrence in one, necessitating resection; this figure gives a recurrence rate following simple detorsion for this series of 20 per cent. The figure may require upward revision in the future, inasmuch as two patients have not been followed for a sufficient time

3. Sweet, R. H.: Volvulus of the Cecum: Acute and Chronic, with Reports of Eight Cases, New England J. Med. **213**:287-293 (Aug.) 1935.

to classify them as cured. This consideration is emphasized by the fact that the one reported recurrence was encountered seven years after simple detorsion at the clinic.

Colostomy of the transverse colon unaccompanied with resection was done in one case, and the patient died shortly after operation. Resection was carried out in nine cases. In eight of these, the procedure of choice was an extraperitoneal operation followed in several weeks by closure of the double-barreled colonic stoma (figure). Resection and primary colocolostomy was undertaken in one case. There were three postoperative deaths in this group, giving a postresection mortality figure of 33 per cent. In considering this high figure for postoperative

Surgical specimen in a case of volvulus of the sigmoid colon in which obstruction was complete and of the closed loop variety, with grade 2 dilatation of the proximal portion of the colon. The specimen measured 75 cm. in length and 11 cm. in diameter. The bowel was viable. Extraperitoneal resection (clamp method) and complemental colostomy of the transverse colon were withstood well. The patient was dismissed from the hospital, with the colonic stomas closed, four weeks after the initial operation. The patient was living and well three years later and had had no further difficulty.

fatality, one must consider the fact that this group included those with high grades of obstruction and infarction of the bowel and mesentery. Among the nine cases of resection, obstruction was incomplete in four and complete in five; and the bowel was infarcted in three of the latter. One death followed resection of an incompletely obstructed sigmoid, while two resulted from removal of a completely obstructed and infarcted segment. In other words, two of the three patients with infarction of the bowel died after resection. This concurs with the experience

of Perlmann,[4] who found the postresection mortality rate in the presence of infarction about double that for the entire group.

Such forbidding figures for postresection fatality in the presence of infarction emphasize the serious consequences of conservative procedures which invite a recurrence that may cause the patient to be subjected to a resection, not of election but of desperation. It has already been noted in this series that incomplete obstruction with subacute manifestations involved chiefly patients in the younger decades, whereas complete obstruction with acute manifestations affected principally those in the older age groups. The obvious deduction from this age differential is that the acute form with complete obstruction and frequent infarction represents the end result of the subacute form with partial obstruction. It is for the subacute form that conservative operations are most frequently performed. The chances are that in this group resection as an elective procedure following detorsion would, by its elimination of recurrence, materially lower the over-all mortality rate.

The extraperitoneal operation is undoubtedly the procedure of choice in all cases, and particularly in the presence of more than moderate degrees of obstruction. In case of concomitant dilatation of the proximal part of the colon, complementary colostomy of the transverse colon or temporary catheter colostomy is indicated. Resection and primary anastomosis would be unwise in the presence of obstruction and without preoperative preparation of the bowel. Recent information given by Bruusgaard [5] on proctoscopic intubation might mean that after relief from the immediate episode the bowel could be prepared and anterior resection carried out as an elective procedure.

In every case in our series an abnormally long sigmoid flexure was observed at operation. The redundant sigmoid undoubtedly is the common denominator in all cases of volvulus. In all probability the extreme measurements observed in the older age groups at the operating table represent the end result of repeated volvulus in a flexure which, to begin with, was congenitally overlong.

Production by the volvulus of double points of obstruction in the proximal and distal parts of the sigmoid with the formation of an isolated loop was the rule in cases in which occlusion of the bowel lumen was complete. Furthermore, distention of the colon proximal to the twist was observed only in cases in which the obstruction was not of the closed loop type or when the patient was seen several days after the onset of symptoms.

Microscopic examination revealed notable infarction of the bowel wall and its mesentery in four of the six cases of complete obstruction, whereas there was no instance of infarction when obstruction was incomplete. The incidence of infarction for the entire series, then, was 25 per cent, while in the presence of complete obstruction it was 66 per cent. Three of the patients with infarction of the sigmoid died postoperatively (two after resection and one after colostomy without resection), giving a postoperative mortality rate in the presence of infarction of 75 per

4. Perlmann, J.: Klinische Beiträge zur Pathologie und chirurgischen Behandlung des Darmverschlusses, Arch. f. klin. Chir. **137**:245-264, 1925.

5. Bruusgaard, C.: Volvulus of the Sigmoid Colon and Its Treatment, Surgery **22**: 466-478 (Sept.) 1947.

cent. It is interesting to note that in these four cases the gross diagnosis of gangrene was made in one at operation and in one at necropsy. Of the other two the surgeon regarded the viability of the bowel as questionable in one and as obviously compromised in the other.

The high incidence of infarction in the presence of complete obstruction emphasizes certain considerations. First, the patients with acute manifestations should have the benefit of immediate operative intervention once the diagnosis is established or entertained. Secondly, patients with subacute manifestations should be considered candidates for radical removal of the redundant sigmoid in order to forestall the ultimate development of an acute episode with complete obstruction, infarction of the flexure and probably death.

In seven of the cases it was the opinion of the surgeon or the pathologist that the large dilated sigmoid represented a localized megacolon (megasigmoid) which had undergone rotation on its mesenteric axis. Throughout the literature megasigmoid is mentioned with varying emphasis as a predisposing cause of volvulus. Is the large, dilated and sometimes hypertrophied sigmoid a true megacolon or simply an acquired megacolon the result of chronic or recurrent obstruction from repeated volvulus? The latter presumption would seem more logical, but the question arises as to how a true megacolon can be differentiated from a pseudomegacolon. Weeks [6] described the microscopic picture of megacolon as that of hypertrophy of the circular musculature. Hypertrophy of the circular musculature also occurs, however, in pseudomegacolon secondary to partial or recurrent obstruction. Whitehouse,[7] in a study of the myenteric plexus in congenital megacolon, found that the ganglions of the myenteric plexus were absent in the distal part of the colon in 100 per cent of the cases studied. The ganglions were present in the descending colon in 100 per cent, and the commonest type of transition between the distal segment and the descending colon was an abrupt change from normal to complete absence. Microscopic examination of sections from the lower portion of each surgical or necropsy specimen in this series revealed the ganglions of the myenteric plexus to be normally present. This finding indicates that the so-called "megasigmoids" in this series were acquired from chronic obstruction incident to repeated twists and did not represent congenital types which had secondarily rotated on the mesenteric axis.

CONCLUSIONS

1. Volvulus of the sigmoid colon more commonly affects males.

2. It probably accounts for about 20 per cent of all intestinal torsions and 2 per cent of all intestinal obstructions in this country.

3. The acute form with complete obstruction affects chiefly the elderly, whereas the subacute form with incomplete obstruction occurs in a younger age group.

4. Two thirds of the patients with complete obstruction may be expected to have marked infarction of the sigmoid and its mesentery.

6. Weeks, C.: Volvulus of a Sigmoid Megacolon, Ann. Surg. **94**:1050-1060 (Dec.) 1931.

7. Whitehouse, F. R.: Study of the Myenteric Plexus in Eleven Cases of Congenital Megacolon, Thesis, University of Minnesota Graduate School, 1947.

5. Resection of the twisted redundant sigmoid offers the only prospect of cure. The high postresection mortality rate (33 per cent) is accounted for by the fact that the group for which resection is done includes the high grade obstructions and the infarcted sigmoids. Resection in the presence of infarction carries a mortality rate of 66 per cent. Simple detorsion is followed by a high recurrence rate (20 per cent or more), and a recurrence may necessitate resection later in the presence of infarction.

6. The redundant sigmoid is the common denominator in all cases of volvulus.

7. Megasigmoid is not a cause of volvulus. The dilated and hypertrophied sigmoid is the result of chronic and recurrent obstruction of repeated volvulus.

HOMOLOGOUS TRANSPLANTATION OF TISSUES

A Review of the Literature

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AND
S. W. SMITH, M.D.
LOS ANGELES

CONTINUED growth and permanent survival of tissues transplanted from one human being to another have been unmistakenly demonstrated only when the transfer has been made between identical twins.

Relatively acellular, inert tissues, such as bone and cartilage, have been used satisfactorily as homografts, but they serve only as a bridge or supporting structure for the invading tissues of the host. The cells of the graft die and are replaced by invading cells of the recipient. Although satisfactory clinical results are obtained, such grafts cannot be considered to have survived permanently. Homografts of corneal tissue have given satisfactory, permanent results in many cases. The cornea also is a relatively acellular tissue. Maumenee and Kornblueth [1] have demonstrated that the majority of the stromal cells continue to live in the graft and do not show a massive degeneration or replacement at any time after transplantation. They are supplemented, at least to a limited extent, by the newly formed keratoblasts from the recipients' macrophages. The epithelium is replaced by migrating epithelial cells from the recipient cornea. The endothelium may be replaced by the uninjured cells of the graft or by migrating cells from the recipient cornea. There are, however, other factors involved in the transplantation of corneal grafts, such as lack of lymphatic drainage and lack of inherent blood supply in the graft. These factors, which are not encountered in other types of grafts, may alter the response of corneal transplants so that they do not behave as grafts of other tissues.

Much of our information concerning the homotransplantation of tissues in human beings has been obtained from observation of grafts of skin and of endocrine gland tissue. In contrast to the cells of bone and cartilage, the cells of such grafts must retain their vitality and their ability to grow and reproduce if the graft is to be effective.

The confusion of the past in regard to the survival of such homografts has in recent years been replaced by the universal acceptance that homotransplants do not remain permanently viable, and attention has been directed toward a study of the mechanism of destruction and means of combating such destruction. The clinical value of skin homografts during their period of temporary survival has also been

From the Department of Surgery, University of California at Los Angeles School of Medicine.

1. Maumenee, A. E., and Kornblueth, W.: Symposium: Corneal Transplantation; Physiopathology, Tr. Am. Acad. Ophth. **52**:331, 1948

studied. Anyone who has tried to make repeated observations over a period of weeks or months of a certain area of grafted skin, particularly when the graft has been applied to a granulating surface, can readily appreciate the difficulties of the early investigators in making an accurate appraisal of the survival time of homografts.

Almost all skin homografts, if properly applied, will "take" primarily and persist for a period of from two weeks to two months. If the graft is small and surrounded by normal tissue, the invasion of the tissues of the recipient into the graft may keep pace with the process of destruction so that there is no gross evidence of necrosis of the graft. This process of invasion of the graft by host tissues has several times given rise to false reports of the permanent survival of skin homografts. In larger granulating wounds, it is difficult to obtain accurate observation because of contraction of the margins of the defect, ingrowth of epithelium from the surrounding skin edge and ingrowth of regenerated epithelium from viable epithelial structures such as sweat glands and hair follicles in the base of the defect beneath the homograft. These difficulties are encountered particularly when the period of study must extend over many weeks.

Although the actual mechanism of destruction remains in doubt and methods have not been developed for preventing the ultimate necrosis of homografts, a great deal of interesting data has been accumulated concerning the behavior of cells transferred from one person to another.

STUDIES MADE IN THE INVESTIGATION OF BEHAVIOR OF HOMOGRAFTS

I. *Studies on the Use of Random Grafts.*—About the beginning of the century, as the use of free skin grafts became popular, differences between homologous and autogenous grafts were not appreciated. Grafts of all types were used, and successful homotransplants were frequently reported. Davis,[2] Masson,[3] Bartens,[4] Baldwin[5] and Dyke[6] reported numerous successful homografts, although the evidence presented in their articles is unconvincing in the light of our present knowledge of the behavior of these transplants.

II. *Parabiotic Studies.*—It is possible permanently to unite the bodies of two animals by operation if they are members of the same highly inbred strain. However, Padgett and Stephenson[7] were unsuccessful in their attempt to obtain permanent parabiotic union in dogs. In these studies, they used both litter mates and odd dogs. Such procedures in human beings, even between members of the same family, likewise are not permanently successful. Gillies[8] has reported the case of an infant with a large skin defect of the leg which was joined by a skin flap to the thigh of the mother. The flap originally healed in place satisfactorily but began to show evidence of breakdown about the edges at about the time it was divided from the mother. It subsequently became entirely necrotic.

2. Davis, J. S.: Some of the Problems of Plastic Surgery, Ann. Surg. **66**:89, 1917

3. Masson, J. C.: Skin Grafting, J. A. M. A. **70**:1581 (June 1) 1918.

4. Bartens: Transplantation der Haut von einer Leiche, Berl. klin. Wchnschr. **25**:649, 1888.

5. Baldwin, H. A.: Skin Grafting and Blood Groups, M. Rec. **98**:686, 1920.

6. Dyke, S. C.: Blood Grouping and Its Clinical Applications, Lancet **1**:581, 1922.

7. Padgett, E. C., and Stephenson, K. L.: Plastic and Reconstructive Surgery, Springfield, Ill., Charles C Thomas, Publisher, 1948, p. 46.

8. Gillies, H. D., in Trusler, H. M., and Cogswell, H. D.: The Question of Homoplastic Skin Grafting, J. A. M. A. **104**:2076 (June 8) 1935.

Reinhard and Lauer [9] performed a similar procedure between a 14 year old girl and her brother. The flap healed in place, but on the eighth postoperative day the recipient suffered from severe syncope and recovered only after removal of the flap. The blood of the recipient was type A and that of the donor type O. It was suggested that incompatibility of the blood groups was responsible for the severe reaction of the recipient.

III. *Compatibility Studies.*—As surgeons became dissatisfied with the results of homografts and certain men of wide experience, such as Lexer,[10] Gatch,[11] Schoene [12] and Perthes [13] began to express their skepticism of the ultimate survival of homografts, various attempts were made to find compatible donors and recipients in order to improve the results of homografting.

One of the first suggestions in this regard was that there might be a genetic compatibility between members of the same family, and it is in this group that the only authentic permanent survivals of homografts have been reported. Bauer,[14] Padgett,[15] Brown,[16] Schattner [17] and Converse [18] have all recorded authentic instances of permanent survival of skin homotransplants between identical twins.

Two instances of successful homotransplantation of skin from father to son (Wolf [19]) and from both mother and father to son (Kearns and Reid [20]) have been reported. However, all other cases of tissue interchanged between members of the same family, other than in monozygotic twins, have been reported as uniformly unsuccessful.

With the introduction of the principles of blood groups, it was hoped that the same factors might govern the compatibility of other tissues, and several reports (Shawan,[21] Baldwin,[5] Dyke [6] and Kubányi [22]) appeared of successful interchange of skin grafts between persons of compatible blood groups. Unfortunately these

9. Reinhard, W., and Lauer, A.: Gefahren der gestielten Hautlappenverpflanzung, bei der Homoioplastik, Deutsche Ztschr. f. Chir. **254**:661, 1941.

10. Lexer, E.: Die freien Transplantation, in von Bruns, P.: Die neue deutsche Chirurgie, vol. 2, 1913.

11. Gatch, W. D.: Report of a Case of Extensive Thiersch Skin Graft, Bull. Johns Hopkins Hosp. **22**:84, 1911.

12. Schoene, G.: Die heteroplastische und homeoplastische Transplantation, Berlin, Springer-Verlag, 1912.

13. Perthes, G.: Ist Homöoplastische Hautverpflanzung unter Geschwistern der Autotransplantation gleichwertig? Zentralbl. f. Chir. **44**:426, 1917

14. Bauer, K. H.: Homoiotransplantation von Epidermis bei eineügen Zwillingen, Beitr. z. klin. Chir. **141**:442, 1927.

15. Padgett, E. C.: Is Iso Grafting Practicable? South, M. J. **25**:895, 1932

16. Brown, J. B.: Homografting of Skin with Report of Success in Identical Twins, Surgery **1**:558, 1937.

17. Schattner, A.: Report of Isograft Transplants in Identical Twins, Arch. Otolaryng. **39**:521 (June) 1944.

18. Converse, J. M., and Duchet, G.: Successful Homologous Grafting in War Burns Using Identical Twin as Donor, Plast. & Reconstruct. Surg. **2**:342, 1947.

19. Wolf, F.: Beitrag zur homoioplastichen epidermis Transplantation, Med. Klin. **41**:350, 1946.

20. Kearns, J. E., Jr., and Reid, S. E.: Successful Homotransplantation of Skin from Parents to Son, Plast. & Reconstruct, Surg. **4**:502, 1949.

21. Shawan, H. K.: Principle of Blood Grouping Applied to Skin Grafting, Am. J. M. Sc. **157**:503, 1919.

22. Kubányi, A.: Hauttransplantationsversuche auf Grundlage der Isoagglutination, Arch. f. klin. Chir. **129**:644, 1924.

reports, when critically analyzed, do not present authentic evidence of permanent homograft survival. More recent reports, other than that of Kearns and Reid [20] in which the mother, father and son were all type O, have demonstrated that homografts do not survive, even when donor and recipient have compatible bloods, typed not only for the usual groups but also for the M and N subgroups. In Wolf's [19] case of successful homograft the donor and recipient were incompatible.

In a case which we have studied (Longmire and others [23]), on a recipient with group B blood was grafted skin from seven group A donors, two group B donors and nine group O donors. We could detect no relationship between the blood groups and the initial "take" or survival time of the grafts. None of the grafts was permanently successful.

IV. *Studies on Skin Groups.*—Although skin transfer does not follow the principles of blood groups, it might be considered that there are other or additional similar factors governing the compatibility of skin transfer and that there are skin groups just as there are blood groups. Definite evidence that skin groups exist has not been obtained. Medawar [24] has investigated this possibility in rabbits and concluded that there are at least seven independently combined antigens governing the grafting reaction of the skin of rabbits, and he has suggested the corollary that a rabbit may belong to one of at least 127 skin transplantation groups. We have obtained some data on this theory in man and have found evidence that if there are skin groups in man it is unlikely that there are less than 23 such groups (Longmire, Stone, Daniel and Goon [23]).

V. *Experiments with Infant Tissues.*—It has been shown that tissues can be interchanged between individuals of species low in the phylogenetic scale and between embryos of higher species. At least four reports have appeared, one as recently as 1943 (Sachs and Goldberg [25]), of infant foreskins successfully used as homografts (Lucas,[26] McNealy, cited by Ashley,[27] and Ashley, 1937). Our investigations, however, fail to confirm the theory that infant tissues may be successfully used as homografts.

VI. *Studies on Altered Tissues.*—Having failed to find any trace of compatibility between tissues of different individuals, various investigators have considered the possibility of altering the reaction of the recipient so that homotransplanted tissues might survive.

First, let us consider attempts that have been made to alter the tissues of the graft.

A. Altered Donor Tissues: 1. Tissues altered by freezing. Baxter and Entin [28] transplanted, between 29 different persons, 38 pieces of skin which had been cooled to various temperatures ranging from 45 to —108 F. for various periods

23. Longmire, W. P., Jr.; Stone, H. B.; Daniel, A. S., and Goon, C. D.: Report of Clinical Experiences with Homografts, Plast. & Reconstruct. Surg. **2**:419, 1947.

24. Medawar, P. B.: A Second Study of the Behavior and Fate of Skin Homografts in Rabbits, J. Anat. **79**:157, 1945.

25. Sachs, A. E., and Goldberg, S. L.: Foreskin Isografts, Am. J. Surg. **60**:255, 1943.

26. Lucas, R. C.: On Prepuce Grafting, Lancet **2**:586, 1884.

27. Ashley, F.: Foreskins as Skin Grafts, Ann. Surg. **106**:252, 1937.

28. Baxter, H., and Entin, M. A.: Experimental and Clinical Studies of Reduced Temperatures in Injury and Repair in Man: Structure and Potentialities of Human Skin in Temperature Control and in Defense Against Thermal Trauma, Plast. & Reconstruct. Surg. **2**:569, 1947.

from four hours to 308 days. No correlation was found between either the severity of the degree of cooling or the duration of exposure and the length of survival. All homografts failed to survive. The rapidity of disintegration varied, but no homograft survived beyond two to three weeks subsequent to grafting. Susceptibility to infection was conspicuous in this series of grafts. The investigators felt that refrigeration of homografts shortened the survival time irrespective of the length of exposure or the severity of cold. These experiments would indicate that reduced temperatures do not produce physicochemical changes in the cells of the graft which are beneficial in regard to survival of the homograft.

2. Tissues altered by heating. Rouse [29] believes that causing hyperemia of the donor site by application of heat or by mechanical means increases the chances of "take" of the autograft. Peters [30] has found 50 to 55 C. for 30 to 60 seconds a critical temperature for damage of skin cells in experimental animals. Kiskadden and McDowell [31] have heated guinea pig skin homografts at temperatures of 114 to 120 F. for 30 minutes before transplantation. Although at present their experiments are incomplete, there is some evidence to suggest that skin homografts so treated survive for 60 to 70 days and longer after transplantation. However, it would seem difficult to postulate any significant alteration of the physicochemical properties of cells occurring with temperatures lower than that which will produce actual death of the cells.

Heating or boiling of homologous cartilage transplants has frequently been used with satisfactory clinical results. The problem here, however, is different from the problem in cases in which it is desired to produce grafts with viable reproductive cells.

3. Tissue culture methods. Stone, Owings and Gey [32] have attempted to alter the tissues of the graft in such a way that they would no longer be antigenic to the host, by growing the tissues to be transplanted in tissue culture with the recipient's serum, hoping that the donor cells might thereby become adapted to their subsequent environment. They homotransplanted thyroid and parathyroid tissue in a series of 11 dogs. Five, they felt, showed definite unquestionable long-standing "takes." Photomicrographs are presented of viable thyroid tissue 148 days after grafting. In human beings ten grafts were applied, only two of which, at the time of their report, had gone long enough to be of significance. Both of these were considered successful.

The same authors presented a year later,[33] four successful cases of homotransplants of thyroid or parathyroid tissue. Since that time, however, the matter has not been pursued further, nor have similar studies been made of skin homografts.

4. Embryo transplants. Various types of tumor cells have been grown in chick embryos, both on the membranes and in the organs of the chick, after intravenous injection. Goodpasture, Douglas and Anderson [34] have been able to grow pieces

29. Rouse, P.: The Activation of Skin Grafts, J. Exper. Med. **83**:383, 1946.

30. Peters, R. A.: Biochemical Lesions in Thermal Burns, Brit. M. Bull. **3**:81, 1945.

31. Kiskadden, W. S., and McDowell: Personal communication to the authors.

32. Stone, H.; Owings, J., and Gey, G. O.: Transplantation of Living Grafts of Thyroid and Parathyroid, Ann. Surg. **100**:613, 1934.

33. Stone, H.; Owings, J., and Gey, G. O.: Living Grafts of Thyroid and Parathyroid, Surg., Gynec. & Obst. **60**:390, 1935.

34. Goodpasture, E. W.; Douglas, B., and Anderson, K.: Study of Human Skin Grafted upon the Chorio-Allantois of Chick Embryos, J. Exper. Med. **68**:891, 1938.

of human skin on the membranes of the chick embryo for as long as 14 days. They suggest the possibility of transferring such tissues back to man but report no instance in which this was actually done.

5. Tumor tissue transplants. Attempts to transplant tumor tissue from one adult human being to another have also failed. We have attempted to transfer a small squamous cell carcinoma of the skin from one person to another with a similar type of skin neoplasm. There was an initial "take" of the graft, but the lesion did not persist; eventually, regenerated epithelium from the margin of the defect grew under the graft and the area healed with normal scar tissue.

We likewise homotransplanted a small portion of fresh, parathyroid tumor tissue into the pectoral muscle of a patient with hypoparathyroidism. An immediate effect of the graft was evidenced by a marked rise of the serum calcium of the recipient the day following transplantation. The effect was sustained for only a week, however.

B. Altered Host Reaction: Attempts to alter the reaction of the host to the foreign tissue have not been numerous. As the mechanism of the immune reaction in human beings is better understood, other avenues of investigation will become apparent.

1. Desensitization of the host. Desensitization of the recipient by the injection of large doses of donor serum was found by Baetzner and Beck [35] to be effective in prolonging the survival time of homografts. On the other hand, Rohde [36] attempted to lower the resistance of the recipient animal toward skin homotransplants through previous treatments with blood plasma, serum, skin extracts and skin autolysates. Homografts usually survived longer on the untreated recipients than on the treated ones.

As desensitization is apt to be temporary in its effect, it seems unlikely that the procedure would be of value in assisting the prolonged survival of homografts.

2. Irradiation. Loeb's [37] theory of the cellular destruction of homografts is one explanation which has been advanced for the destruction of these transplants. He states: "As to the action of lymphocytes, there can be no doubt that they actually help to destroy the transplant. It is largely by means of cellular reactions on the part of the host that the destruction of homotransplants is accomplished." The significant invasion of round cells seen in microscopic sections of homografts as necrosis sets in certainly draws attention to the possible role of the lymphocyte in the mechanism of destruction of homografts. Irradiation has been used as a means to reduce the numbers of lymphocytes, a possible method of inducing homograft takes. This procedure has been unsuccessful, however. Rabinovici [38] produced a marked reduction in the circulating lymphocytes of rats for a period of 10 to 11 days with a single roentgen ray exposure of 500 r, but homografts of skin transplanted 40 hours after irradiation of the recipient suffered the same fate of eventual

35. Baetzner, W., and Beck, S.: Über Homoiotransplantation, Zentralbl. f. Chir. **55**:272, 1928.

36. Rohde, C.: Über Versuche zur Überwindung der Anheilungsschwierigkeiten homoplastischer Transplantate, Beitr. z. klin. Chir. **134**:111, 1925.

37. Loeb, L.: Transplantation and Individuality, Physiol. Rev. **10**:547, 1930; The Biological Basis of Individuality, Science **86**:1, 1937.

38. Rabinovici, N.: The Fate of Skin Homotransplants Performed on Previously X-Rayed Rats, Plast. & Reconstruct. Surg. **2**:413, 1947.

destruction as transplants to nonirradiated animals, in spite of the reduction in the number of circulating lymphocytes. Later work (Ehrich, Drabkin and Forman [39] and Darcy [40]) would implicate an additional cell possibly entering into this destructive mechanism along with the lymphocyte. This cell resembles a plasma cell in morphology and staining characteristics.

3. Antihistaminic drugs. As histamine is frequently released in antigen-antibody reactions involving the skin, Foster and Hanrahan [41] postulated that possibly it was released by the antigen-antibody reaction between the foreign tissue and that of the host and that histamine so released might play a role in the destruction of the homograft. Pyribenzamine® (tripelennamine), an antihistaminic drug, was given to the recipient of a homograft. A split thickness graft from a white man was placed in a full thickness skin defect on a Negro woman. The recipient received pyribenzamine® therapy for 60 days, at which time the graft was apparently viable. A biopsy at this time showed living skin with hair follicles and sweat glands. The surface epithelium might represent invading host cells; the hair follicles and sweat glands deep in the graft must certainly have represented donor tissue. There was no gross change in the appearance of the graft at the end of 90 days. As their experience was limited to this single case, the authors drew no conclusions but suggested that further studies be made of the power of the antihistaminic drugs to suppress the destruction of homografts.

VII. *Attempts to Circumvent Host Reaction.*—Rich and Follis [42] were able to produce an Arthus type of sensitivity reaction to antigen in the cornea of a sensitized animal only after the cornea had been vascularized. They concluded that in the Arthus type of hypersensitivity there is vascular sensitivity, but the cells of the tissues at large are not sensitized. Tissue death in the Arthus reaction results primarily from impairment of nutrition due to vascular damage and to clogging of the tissue spaces with the exudate and hemorrhage.

Medawar [43] postulates a different view of the function of the vascular supply in the antigen-antibody reaction of the homograft. He feels that the blood vessels are important from the standpoint of transporting the destructive substances in the plasma or blood cells but that it is not lack of nutrition from a damaged vascular supply which causes the destruction of the homograft.

In any event, it has been found that a large variety of tissues, both autogenous and homologous, will survive when transplanted into the anterior chamber of the rabbit's eye, and it would appear that the destructive response to homologous tissue is less intense at this site than elsewhere in the body. Medawar has found that homologous skin grafts, even in sensitized animals, survive in the anterior chamber of the eye unless they become vascularized and are thus brought into contact with

39. Ehrich, W. E.; Drabkin, D. L., and Forman, C.: Nucleic Acids and the Production of Antibody by Plasma Cells, J. Exper. Med. **90**:157, 1949.

40. Darcy, D. A.: Plasma Cells in the Reaction Against Rabbit Tissue Homografts, Nature, London **163**:98, 1949.

41. Foster, D. G., and Hanrahan, E. M.: Observations on a Skin Homograft After 60 Days of Pyribenzamine Therapy, Bull. Johns Hopkins Hosp. **82**:501, 1948.

42. Rich, A. R., and Follis, R. H., Jr.: Studies on Site of Sensitivity in Arthus Phenomenon, Bull. Johns Hopkins Hosp. **66**:106, 1940.

43. Medawar, P. B.: Immunity to Homologous Grafted Skin: III. The Fate of Skin Homografts Transplanted to the Brain, to Subcutaneous Tissue and to the Anterior Chamber of the Eye, Brit. J. Exper. Path. **29**:58, 1948.

the substance circulating in the blood stream, such process producing the necrosis of the graft. On the other hand, the extensive experience of Greene [44] with anterior chamber transplants indicates that none of these grafts survives unless a blood supply is established.

VIII. *Experiments on Grafting to Brain Tissue.*—It has been suggested that since the central nervous system does not contain lymphatic vessels homografts into the substance of the brain might not elicit the antibody response produced by grafts in other areas. It has been established by Shirai [45] and Murphy [46] independently that heterologous tumors will survive and grow in the brain and by Tansley [47] that embryonic rat eyes transplanted into the brains of two day old rats will do the same. In the work of the latter it was found that healthy eye tissue survived for 294 days when graft and host were of the same strain. The longest survival time of a graft made into a different strain was 167 days. Siebert [48] implanted homologous thyroid tissue into the subcutaneous tissue and into the brains of guinea pigs in separate experiments and found that the grafts survived longer in the brain than under the skin. He noted, however, that the survival of the former was less than that of autogenous grafts to the same sites. On the basis of the work of Shirai,[45] Murphy [46] and Tansley,[47] Medawar postulates that skin homografts enjoy prolonged or indefinite survival when grafted to the brains of nonimmunized animals. He performed a series of experiments in which a graft was transplanted to the left cerebral hemisphere and, simultaneously, to a raw field on the chest 16 to 20 days after preliminary specific immunization. He found that the orthotropic control graft on the chest became completely necrotic in the 10 days allowed to pass between transplantation and removal at autopsy. Medawar concludes on the basis of the foregoing that "skin homografts transplanted to the brain submit to, but cannot elicit an immune state." Thus, it has not been definitely established that adult skin homografts will persist in the brains of nonimmunized animals. The possible continued survival of homografts to the central nervous system and the role played by the absence of lymphatic vessels in the brain deserve further study.

Within the past year, Beal and Lockwood [49] have carried out a series of experiments involving the homologous transplantation of adult organs to the brains of unrelated adult cats and rats. This work, outlined as follows, has met with almost consistent failure:

Experiment 1. Homologous adult rat adrenal tissues were transplanted to the brains of adult cats which were simultaneously bilaterally adrenalectomized.

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44. Greene, H. S. N.: Participation of Anterior Chamber of Eye in Resistance Phenomena Related to Tumor Growth, Cancer Research **2**:669, 1942.

45. Shirai, Y.: Transplantation of Rat Sarcoma into Brain, Japan M. World **2**:14, 1921, cited by Murphy, J. B.: The Lymphocyte in Resistance to Tissue Grafting, Malignant Disease and Tuberculous Infection: An Experimental Study, Monograph 21, New York, Rockefeller Institute of Medical Research, 1926.

46. Murphy, J. B.: The Lymphocyte in Resistance to Tissue Grafting, Malignant Disease and Tuberculous Infection: An Experimental Study, Monograph 21, New York, Rockefeller Institute of Medical Research, 1926.

47. Tansley, K.: The Development of the Rat Eye in Graft, J. Exper. Biol. **22**:221, 1946.

48. Siebert, W. J.: Auto and Homoiotransplantation of Thyroid Gland into Brain of Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **26**:236, 1928.

49. Beal, J., and Lockwood, R.: Unpublished data.

Adrenal cortical extract was then administered to the animals. Three of them survived 17, 22 and 29 days, respectively, and when the graft remnants were examined histologically, no viable tissue was found.

Experiment 2. Homologous adult rat adrenal tissues were transplanted to the brains of adult animals which were simultaneously bilaterally adrenalectomized. This operation was not followed by any supportive therapy. Of 12 rats receiving the transplants, only one survived for a significant period (85 days), and in this one viable adrenal tissue was found. The possibility that in the latter case both donor and recipient may have been litter mates could not be eliminated, however.

Experiment 3. Homologous adult rat adrenal tissues were transplanted to the brains of nine adult rats which were bilaterally adrenalectomized three and four days after transplantation. Results in this group are not conclusive but appear to be transplantation failures.

Experiment 4. Eight adult cats were bilaterally oophorectomized. This operation was followed by transplantation of homologous adult ovarian tissue to the brains, performed at varying intervals of two to 33 days after oophorectomy. The cats were given 5 mg. of diphenhydramine hydrochloride (benadryl®). All were killed in two months. No viable ovarian graft tissue was found on section.

These experiments would appear to indicate that adult organ homografts to the brain are unsuccessful and that, at least in a very small group, such transplants are uninfluenced by the antihistaminic drug diphenhydramine hydrocholride.

CLINICAL USE OF HOMOGRAFTS AS A TEMPORARY COVERING

In the absence of any concrete evidence that skin homografts permanently survive, the only indication for the clinical use of such grafts at the present time is as a temporary covering or dressing, usually in cases of severe burns, when autografting is contraindicated.

Although such a use of homografts has been referred to in a number of publications, the method has never been widely used and it is difficult to evaluate its effectiveness from the limited published data. There are few surgeons who regularly graft skin who have not, at one time or another, used skin homografts. At the same time there must be few surgeons who have adopted the practice of using homografts with any degree of regularity, even in severely burned, debilitated patients.

Proponents of the method feel that in a few selected instances the use of homografts may be lifesaving. Patients with large, raw surfaces who have become debilitated may continue a downhill course in spite of intensive therapy unless the infection of the raw surface is eliminated and the loss of protein-rich fluid and blood from the area is stopped. Covering the area with skin homografts is one method whereby this may be accomplished temporarily.

The chief factors which have discouraged the clinical use of homografts include the following: (1) the difficulties of obtaining skin donors, (2) the inconvenience to the donor if a sizable graft is taken, (3) the uncertainty of even a temporary "take" of the graft when the general condition of the recipient is such as to contraindicate autografting, (4) the dangers of a generalized allergic reaction to the foreign skin, (5) the uncertainty of the survival time of the graft if a primary "take" occurs and (6) the undesirable local effects if the homograft begins to "melt away" before the patient is ready for autografting.

Spaeth and Cappriotti [50] have recently reported the case of a 15 year old boy in which bilateral ectropion resulting from ichthyosis congenita was corrected by homografts taken from a donor whose blood matched the recipient's in blood type, Rh, M and N factors. Regardless of whether the grafted tissue permanently survived or whether it served merely as a bridge for invasion of surrounding host tissues, a satisfactory correction of the deformity was obtained. This may indicate another possible use of skin homografts, that is, as replacement tissue in small vital areas when autografting is contraindicated.

We are of the opinion that the indications for the use of homografts as temporary dressings are extremely limited. Although a supply of grafts might be maintained by refrigeration of skin grafts or by removal from fresh cadavers, amputated limbs or operative specimens, the demand for such tissues is so limited that it would not seem practical. As stated previously, Baxter and Entin [28] found that refrigeration of homografts shortened the length of survival of the skin grafts after transplantation, irrespective of the length of exposure or the severity of cold.

In the rare case when homografting is indicated it would seem advisable that fresh grafts be obtained. As the compatibility of blood groups of the donor and recipient has not been found to influence the initial take or the length of survival of the homograft, the skin from any healthy donor may be used. Transmission of the spirochete of syphilis by homografting, although it has not been known to occur, would theoretically be possible, and the same precautions in this regard should be exercised in selecting a skin donor as are used for blood donors.

Since the object of applying the temporary homograft is to obtain as quickly as possible a closed wound, large sheets of split thickness skin should be used rather than "pinch" grafts or "postage stamp" grafts and as much of the denuded area covered at one time as possible.

The development of an acquired immunity to foreign skin in the recipient contraindicates repeated homografting. Not only will the survival time of the homografts be reduced but if the same donor is used more than once there is danger of provoking a severe, generalized allergic reaction such as has been described by Holman,[51] Schoene [52] and others. All the reports which we have reviewed of severe allergic reactions developing in the case of recipients of free homografts were made after the patient had received two or more sets of grafts at different times from the same donor.

After the initial "take," the homografts should be followed closely, inasmuch as they may begin to disintegrate any time after the second week. Beginning destruction will usually be noted first about the edges of the graft or in areas where the epithelium of the graft has spread out over the surrounding host tissues. Such spreading epithelium is usually destroyed first when the process of destruction begins. Another early change is the appearance of small subepithelial blisters which later coalesce, lifting the epithelium off the graft. In grafts from Negroes this

50. Spaeth, E. B., and Cappriotti, O. A.: Heteroplastic and Isoplastic Skin Grafts, Plast. & Reconstruct. Surg. **3**:707, 1948.

51. Holman, E.: Protein Sensitization in Isoskingrafting, Surg., Gynec. & Obst. **38**:100, 1924.

52. Schoene, G.: Die Heteroplastische und homeoplastische Transplantation, Berlin, Springer-Verlag, 1912. Holman, E.: Protein Sensitization in Isoskingrafting, Surg., Gynec. & Obst. **38**:100, 1924.

process is easily recognized as the pigmented layer of the graft is removed. In nonpigmented grafts such changes are less easily recognized. If the destructive process is permitted to advance there is a slow absorption, sometimes over a period of weeks, of collagen and fibrous tissue of the derma. During this period when there is necrotic tissue present local infection usually increases, the granulation tissue base becomes edematous and the local site is in an unfavorable condition to receive the autograft.

After application of the homografts, the patients should be treated vigorously to improve their general condition as quickly as possible so that the homografts can be removed and replaced by autografts before the process of destruction sets in. Unless this is done the advantages gained from the use of homografts will be lost.

COMMENT

In support of the theory that an active acquired immunity to a foreign tissue is the mechanism responsible for the destruction of homografts, Medawar [53] has made a number of interesting observations:

1. The survival time of homotransplanted skin is related to the amount of tissue, or dosage, of grafted skin. Small amounts of grafted tissue survive longer than larger grafts. This may account for the minimal reaction against small homografts and the acellular tissues of bone and cartilage.

2. A second set of homografts between the same donor and recipient are destroyed more rapidly than the first set, supposedly because the recipient has been sensitized to the foreign tissue by the first set of grafts.

3. The host antibody acts on some component of the nucleus of the recipient cells and destruction of the homotransplant starts when the cells of the graft divide.

4. Prior injection into the recipient of donor serum, plasma or red cells does not sensitize the animal to subsequent homografting; however, injections of leukocytes, particularly when given intradermally, are effective in sensitizing the recipient. The results of Medawar suggest that the antigenic property of foreign tissue resides in the nucleus of the cell.

It now appears fairly certain that the immunologic reaction in the adult against any type of antigen, homografts or other, is a systemic reaction that is potentially available throughout the body of the host and that the local reaction which occurs about the site of introduction of the antigen is merely a local manifestation of the system-wide immunity. On the other hand, the evidence presented by Rich and Follis,[42] Goodpasture and Anderson [54] and Medawar [24] indicates that although the potential immunity or sensitivity is present throughout the body, it may be confined to the circulating fluids or circulating cells of the organism and not to each individual cell of the body. For instance, when Goodpasture and Anderson inoculated the skin of an immune chicken with the virus of fowlpox, no relation occurred; however, when a piece of skin was removed from the immune chicken and was grown on the membrane of a chick embryo, inoculation with the virus produced a typical nonimmune reaction in the skin, the reaction indicating that cells of the skin themselves

53. Medawar, P. B.: The Behavior and Fate of Skin Autografts and Skin Homografts in Rabbits, J. Anat. **78**:176, 1944.

54. Goodpasture, E. W., and Anderson, K.: Immunity to Fowlpox Studied by Means of Skin Grafts on Chorioalantois of Chick Embryo, Arch. Path. **30**:212 (July) 1940.

did not possess any power of immunity. Only when the cells of the skin were part of the body of the host and presumably had available the immunologic properties of the circulating fluids or cells of the host's body were they able to resist the fowlpox virus.

It now seens established that adult tissues cannot be successfully interchanged as homografts. However, embryonic tissue in many species can be successfully interchanged. Adult tissues have been successfully grown on chick embryo membranes, and embryonic tissue will survive as a homograft when transferred to an adult of the same species. One might postulate as follows: (*a*) It is likely that the antigenicity of a cell undergoes a fundamental change from embryonic to postembryonic life and that (*b*) the organism develops, as it ages, a specific system endowed with the property of defending the individual against the introduction of certain organic foreign substances into its body.

Considering the information at present available, we may say that when foreign tissues are transplanted some product is liberated, possibly from the nuclei of the cells of the graft, during the normal process of breakdown and repair. This substance stimulates the formation of a specific antibody which is then carried through the blood stream back to the graft, where it reacts with the nuclear substance, during division of the cells, causing destruction of the cells and gradual necrosis of the graft.

SUMMARY

The literature on homologous transplantation is reviewed and clinical and experimental experiences with homografts presented. The acquired immunity theory of destruction of homografts seems to offer a satisfactory explanation for the behavior of homografts. The possible mode of action of the reaction leading to the destruction of homografts is discussed.

IN SURGICAL INFECTIONS

due to Terramycin-sensitive organisms

a partial summary of successfully treated cases

DIAGNOSIS	TOTAL CASES	GOOD RESPONSE
Cellulitis	19	19
Cellulitis with abscess	6	6
Infected laceration	3	3
Human bite infection	1	1
Multiple furuncles	3	3
Carbuncle	2	2
Superficial abscess	5	5
Breast abscess	1	1
Cervical actinomycosis	2	2
Peritonitis	9	9
Gas gangrene	1	1

Pulaski, E. J.: Ann. New York Acad. Sc. *53*:347 (Sept. 15) 1950.

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Dosage: 2 Gm. daily by mouth in divided doses q. 6 h. is suggested for most acute infections. In severe infections, a high initial dose (1 Gm.) or higher daily doses (3 to 6 Gm.) should be used. Treatment should be continued for at least 48 hours after the temperature is normal and acute symptoms subside.

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Within the compact case of this newly designed, readily portable, inexpensive unit, A.C.M.I. engineers have packed a remarkably efficient and ruggedly dependable high frequency unit, amply powered for such electro-surgical procedures as cutting, coagulation, desiccation and fulguration.

The unit provides a vacuum tube cutting outlet, and a spark gap circuit for coagulation, desiccation and fulguration. A selector switch, centrally located, permits quick and unerring selection of tube cutting, coagulating or blended current, as desired. Tube cutting intensity is readily controlled by the right-hand knob, while the spark gap control (for coagulation, desiccation or fulguration) is conveniently located on the left of the panel. Electrodes, cables and other accessories, are carried in the cover of the unit, which is mounted in a durably handsome leatherette case, weighing complete only 32 pounds.

Write for literature

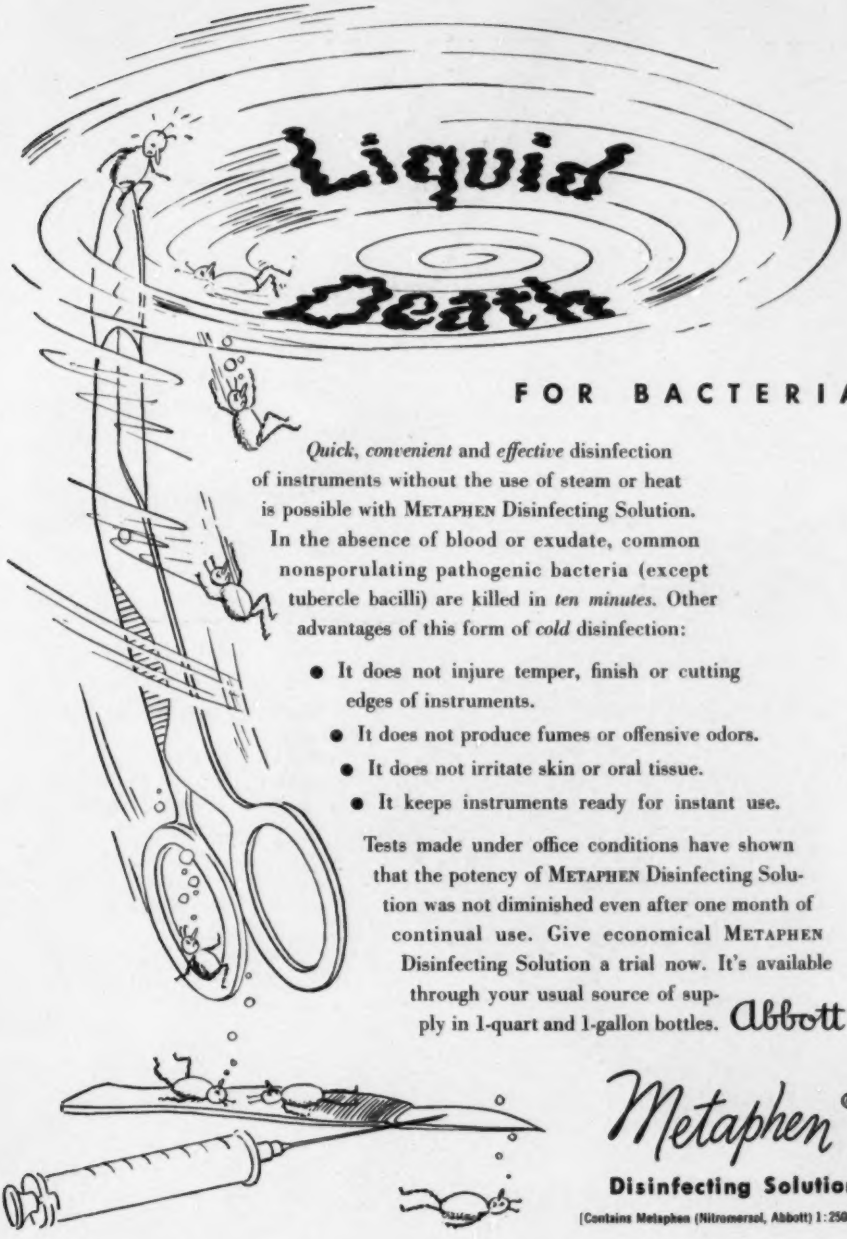
American Cystoscope Makers, Inc.

1341 LAFAYETTE AVE.
FREDERICK J. WALLACE

NEW YORK 59, N. Y.
PRESIDENT

Complete unit supplied in light weight leatherette case

Accessories carried handily in cover



FOR BACTERIA

Quick, *convenient* and *effective* disinfection of instruments without the use of steam or heat is possible with METAPHEN Disinfecting Solution. In the absence of blood or exudate, common nonsporulating pathogenic bacteria (except tubercle bacilli) are killed in *ten minutes*. Other advantages of this form of *cold* disinfection:

- It does not injure temper, finish or cutting edges of instruments.
- It does not produce fumes or offensive odors.
- It does not irritate skin or oral tissue.
- It keeps instruments ready for instant use.

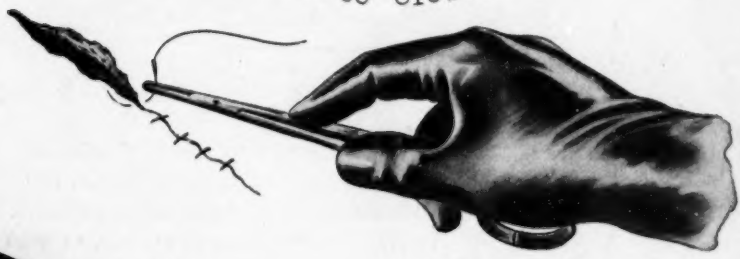
Tests made under office conditions have shown that the potency of METAPHEN Disinfecting Solution was not diminished even after one month of continual use. Give economical METAPHEN Disinfecting Solution a trial now. It's available through your usual source of supply in 1-quart and 1-gallon bottles. Abbott

Metaphen®

Disinfecting Solution

[Contains Metaphen (Nitromersol, Abbott) 1:2500]

...from incision to closure...



spinal anesthesia with

HYDROCHLORIDE

BRAND OF
TETRACAINE HYDROCHLORIDE

- **PROLONGED**
  1½ to 2 hours or more.
- **MARKED MUSCULAR RELAXATION**
- **WELL TOLERATED**
  Little or no fall in blood pressure, low incidence of nausea or post-spinal headache.

Supplied as 1% solution (10 mg. per cc.), ampuls of 2 cc., boxes of 10 and 50; and as "Niphanoid" powder, ampuls of 10 mg., 15 mg. and 20 mg., boxes of 10 and 100.

New: **HYPERBARIC (Heavy) Solution**
For saddle block anesthesia, 0.3% in 6% dextrose, ampuls of 5 cc. (15 mg.), boxes of 10.

In circulatory emergencies . . .
. . . paroxysmal tachycardia
. . . hypotension

NEO-SYNEPHRINE® HYDROCHLORIDE
BRAND OF PHENYLEPHRINE HYDROCHLORIDE

1% Parenteral Solution (10 mg./cc.), 1 cc. ampuls and 5 cc. vials.
0.2% Parenteral Solution (2 mg./cc.), 2 cc. ampuls.

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